(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 2002255263 B2

(54) Title

Novel 1H-indazole compound

(51)[6] International Patent Classification(s)

C07D 231/56 (2006.01)
A61P 21/00 (2006.01)
A61P 25/00 (2006.01)
A61P 25/08 (2006.01)
A61P 25/14 (2006.01)
A61P 25/16 (2006.01)
A61P 25/28 (2006.01)
A61P 29/00 (2006.01)
A61P 37/00 (2006.01)
A61P 43/00 (2006.01)
C07D 231/56 20060101AFI2005100 8BMEP
A61P 21/00 20060101ALI2006052 1BMWO
A61P 25/00 20060101ALI2006052 1BMWO
A61P 25/08 20060101ALI2006052 1BMWO
A61P 25/14 20060101ALI2006052 1BMWO
A61P 25/16 20060101ALI2006052 1BMWO
A61P 25/28 20060101ALI2006052 1BMWO
A61P 29/00 20060101ALI2006052 1BMWO
A61P 37/00 20060101ALI2006052 1BMWO
A61P 43/00 20060101ALI2006052 1BMWO
PCT/JP02/03735

(21) Application No: 2002255263

(22) Application Date: 2002 .04 .15

(87) WIPO No: WO02/083648

(30) Priority Data

(31) Number	(32) Date	(33) Country
2001-116521	2001 .04 .16	JP

(43) Publication Date : 2002 .10 .28

(43) Publication Journal Date : 2003 .04 .17

(71) Applicant(s)

Eisai Co., Ltd.

(72) Inventor(s)

Doko, Takashi; Seshimo, Hidenori; Sato, Nobuaki; Kohmura, Naohiro; Oinuma, Hitoshi; Terauchi, Taro; Ohi, Norihito; Soejima, Motohiro

(74) Agent/Attorney

Davies Collison Cave, 1 Nicholson Street, MELBOURNE, VIC, 3000

(12)特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2002 年10 月24 日 (24.10.2002)

PCT

(10) 国際公開番号
WO 02/083648 A1

(51) 国際特許分類⁷: C07D 231/56, 401/04, 401/06, 401/12, 401/14, 403/04, 403/12, 405/04, 405/12, 405/14, 409/04, 409/06, 409/12, 409/14, 417/12, A61K 31/416, 31/4178, 31/427, 31/428, 31/4439, 31/454, 31/4709, 31/496, 31/50, 31/517, 31/5377, 31/541, A61P 21/00, 25/00, 25/08, 25/14, 25/16, 25/28, 29/00, 37/00, 43/00

(21) 国際出願番号: PCT/JP02/03735

(22) 国際出願日: 2002 年4 月15 日 (15.04.2002)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:
特願2001-116521 2001 年4 月16 日 (16.04.2001) JP

(71) 出願人 (米国を除く全ての指定国について): エーザイ株式会社 (EISAI CO., LTD.) [JP/JP]; 〒112-8088 東京都 文京区 小石川4丁目6番10号 Tokyo (JP).

(72) 発明者; および
(75) 発明者/出願人 (米国についてのみ): 生沼 斉 (OINUMA,Hitoshi) [JP/JP]; 〒305-0053 茨城県 つくば市 小野川7-16 Ibaraki (JP). 大井 紀人 (OHI,Norihito) [JP/JP]; 〒300-0312 茨城県 稲敷郡 阿見町南平台1-12-7 Ibaraki (JP). 佐藤 信明 (SATO,Nobuaki) [JP/JP]; 〒300-0844 茨城県 土浦市 大字乙戸1032-19 Ibaraki (JP). 副島 太啓 (SOEJIMA,Motohiro) [JP/JP]; 〒305-0005 茨城県 つくば市 天久保4-8-7 1-102 Ibaraki (JP). 瀬下 秀則 (SESHIMO,Hidenori) [JP/JP]; 〒335-0021 埼玉県 戸田市 新曽181-1 フレンドリー春大路107号 Saitama (JP). 寺内 太朗 (TERAUCHI,Taro) [JP/JP]; 〒305-0035 茨城県 つくば市 松代3-17-17 パインハイツ201 Ibaraki (JP). 土幸 隆司 (DOKO,Takashi) [JP/JP]; 〒305-0061 茨城県 つくば市 稲荷前9-7 エランドつくばね第2寮204 Ibaraki (JP). 光村 直洋 (KOHMURA,Naohiro) [JP/JP]; 〒300-3262 茨城県 つくば市 蓮沼248-18 Ibaraki (JP).

(74) 代理人: 古谷 馨, 外(FURUYA,Kaoru et al.); 〒103-0007 東京都 中央区 日本橋浜町2-17-8 浜町花長ビル6階 Tokyo (JP).

(81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

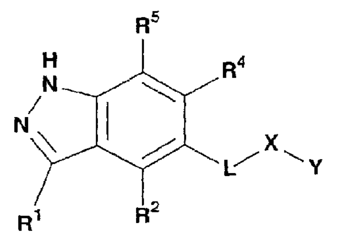
(84) 指定国 (広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
国際調査報告書

2文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(54) Title: NOVEL 1H-INDAZOLE COMPOUND

(54) 発明の名称: 新規1H-インダゾール化合物



(I)

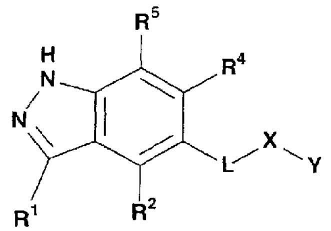
(57) Abstract: A novel 1H-indazole compound having excellent JNK inhibitory activity. It is a compound represented by the following general formula (I), a salt thereof, or a hydrate of either: (I) wherein R^1 means C_{6-14} aromatic cyclic hydrocarbon group; R^2, R^4, and R^5 each independently means hydrogen, halogeno, cyano, etc.; L means a single bond, C_{1-6} alkylene, etc.; X means a single bond, a group represented by -CO-NH- or -NH-CO-, etc.; and Y means C_{3-8} cycloalkyl, a C_{6-14} aromatic cyclic hydrocarbon group, a 5- to 14-membered aromatic heterocyclic group, etc.

[続葉有]

WO 02/083648 A1

(57) 要約:

本発明は、優れたＪＮＫ阻害作用を有する新規な１*H*−インダゾール化合物を提供する。詳しくは、下記一般式で表わされる化合物もしくはその塩またはそれらの水和物を提供する。



（Ｉ）

式中、R^1はC_{6-14}芳香族炭化水素環式基などを意味し、R^2、R^4およびR^5はそれぞれ独立して水素原子、ハロゲン原子、シアノ基などを意味し、Ｌは単結合またはC_{1-6}アルキレン基などを意味し、Ｘは単結合、−ＣＯ−ＮＨ−、−ＮＨ−ＣＯ−で表わされる基などを意味し、ＹはC_{3-8}シクロアルキル基、C_{6-14}芳香族炭化水素環式基または５〜１４員芳香族複素環式基などを意味する。

Description

Novel 1*H*-indazole compounds

Technical Field

The present invention relates to a novel indazole compound having an excellent inhibitory action on protein phosphatase (protein kinase), especially on JNK protein kinase.

Prior Art

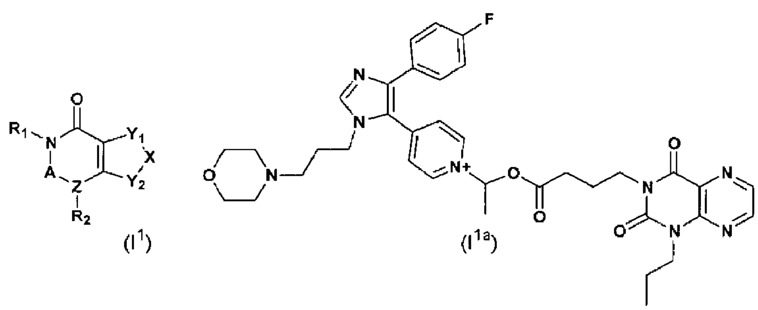
A cascade by action of mitogen-activated protein kinase (hereinafter referred to as "MAPK") is universally presents from yeasts to humans and plays a very important role as one of intracellular signaling pathways. Among such MAPK-related kinases in mammalian cells, three types of kinases, namely, extracellular signal-regulation kinase (ERK), p38, and c-Jun amino-terminal kinase (JNK; or also referred to as stress-activated protein kinases (SAPK)) are particularly well known. SAPKs have been found in rats and are JNK homologues, and it is known that isoform groups thereof each have an amino acid sequence 90% or more equivalent to that of a corresponding isoform group of JNKs (Nature, 369, 156, 1994). A multitude of activators relating to MAPK have been identified recently, and it has been clarified that pathways for activating ERK, p38, and

JNKs play functionally different roles, respectively. Especially, the JNK system is considered to play a role as one of medically and pharmaceutically worthy intracellular signaling pathways for the following reasons. The JNK system is possibly an important signaling pathway that is activated by, for example, stress factors to cells, such as tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), and other cytokines, as well as heat shock, ultraviolet rays (UV), and X-rays, and induces not only cell proliferation and/or differentiation but also apoptosis (cell death) (Science, 270, 1326, 1995). JNKs were first found as a kinase for phosphatasing orylating Ser 63 and Ser 73 at the N-terminus of c-Jun (Nature, 353, 670, 1991), but in recent, it has been clarified that JNKs phosphorylate many transcription factors such as ATF-2 and Elk-1 and regulate their activities (EMBOJ., 15, 2760, 1996). JNKs include three types, JNK 1, JNK 2 and JNK 3. JNK 1 and JNK 2 are expressed in most of tissues, but JNK 3 is particularly highly expressed in the brain (Neuron, 14, 67, 1995; Neuron, 22, 667, 1999). Analyses of knocked out mice lacking JNK 1 or JNK 2 have revealed that these JNKs play important roles in differentiation and/or activation of T cells (J. Exp. Med., 193, 317, 2001). In contrast, it has been reported that knocked out mice lacking JNK 3 have tolerance to spasticity initiated by kainic acid, an excitable amino acid receptor agonist, and that the knocked out mice

lacking JNK 3 do not show apoptosis, which apoptosis is found in hippocampus nerve cells of normal mice after such spasticity (nature 389, 865, 1997). Death of nerve cells due to apoptosis is speculated to play an important role in nerve degeneration processes in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (Experimental Neurology 133, 225, 1995; J. Neurol. Sci. 137, 120, 1996), and results indicating the possibility that JNKs are involved in the nerve cell death have been accumulated (Neuron, 14, 67, 1995; J. Neurochem., 76, 435, 2001).

For example, the following reports have been made on low-molecular substances having JNK inhibitory action.

(1) Compounds represented by the formula having antiinflammatory action, and compounds represented by the formula (I^{1a}) as specific embodiments thereof (WO 00/00491).

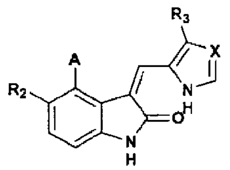


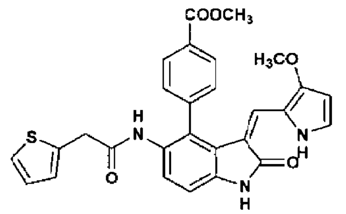
(I^1) (I^{1a})

(2) 4-Aryloxyindole compounds represented by the formula (I^2), and compounds represented by the formula (I^{2a}) as

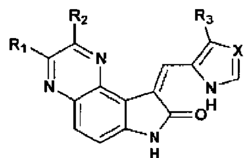
3

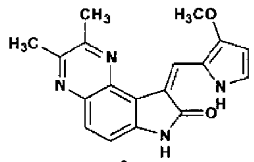
specific embodiments thereof (WO 00/35909).


(I^2)

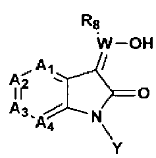

(I^{2a})

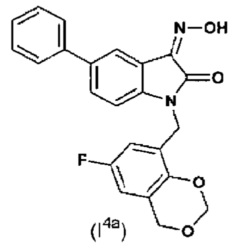
(3) 4,5-Pyrazinoxyindole compounds represented by the formula (I^3), and compounds represented by the formula (I^{3a}) as specific embodiments thereof (WO 00/35921).


(I^3)


(I^{3a})

(4) Compounds represented by the formula (I^4), and compounds represented by the formula (I^{4a}) as specific embodiments thereof (WO 00/64872).

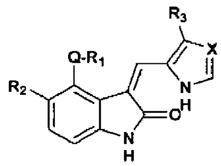

(I^4)

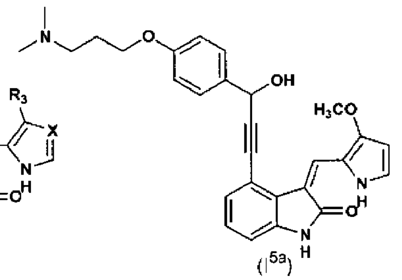

(I^{4a})

(5) Oxyindole derivatives represented by the formula (I^5), and compounds represented by the formula (I^{5a}) as specific

4

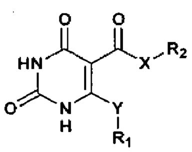
embodiments thereof (WO 00/35906).

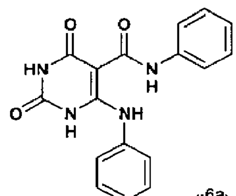




(I^5) (I^{5a})

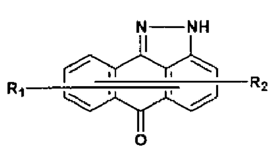
(6) Compounds represented by the formula (I^6) having JNK inhibitory action, and compounds represented by the formula (I^{6a}) as specific embodiments thereof (WO 00/75118).

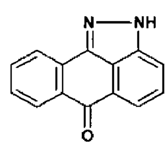




(I^6) (I^{6a})

(7) Compounds represented by the formula (I^7) having JNK inhibitory action, and compounds represented by the formula (I^{7a}) as specific embodiments thereof (WO 01/12609).

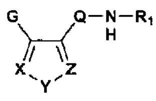




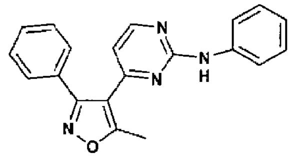
(I^7) (I^{7a})

(8) Compounds represented by the formula (I^8) having JNK

inhibitory action, and compounds represented by the formula (I^{8a}) as specific embodiments thereof (WO 01/12621).

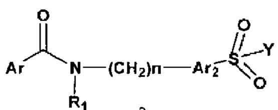


(I^{8})

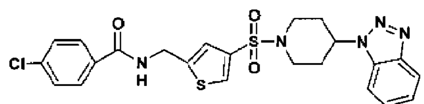


(I^{8a})

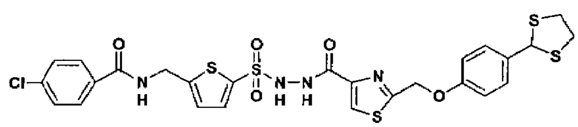
(9) Sulfonamide derivatives represented by the formula (I^{9}), and compounds represented by any of the formulae (I^{9a}), (I^{9b}) and (I^{9c}) as specific embodiments thereof (WO 01/23378, WO 01/23379, and WO 01/23382).



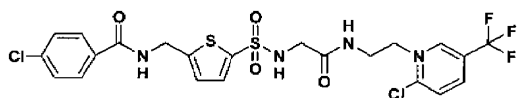
(I^{9})



(I^{9a})

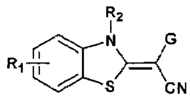


(I^{9b})

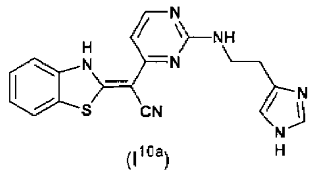


(I^{9c})

(10) Compounds represented by the formula (I^{10}) having JNK inhibitory action, and compounds represented by the formula (I^{10a}) as specific embodiments thereof (EP 01/110957).



(I^{10})



(I^{10a})

In contrast, reports have been made on compounds each having an indazole skeleton in, for example, JP-A 2000-501105, JP-A 2000-198734 and WO 99/23077. However, relations of all these compounds with protein kinases are neither disclosed nor indicated.

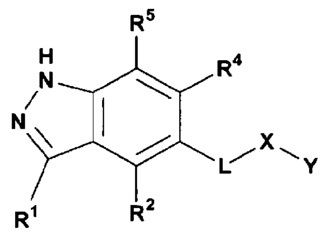
As is described above, the JNK system receives attention as one of important mechanisms relating to activation of various cells, regulation of immunocytes, or apoptosis of neurons induced by various stress signals. Accordingly, compounds exhibiting inhibitory action on the JNK pathway, particularly on JNK protein kinases are expected to be useful as therapeutic agents for various immunologic diseases, inflammatory diseases, and/or neurodegenerative diseases. However, compounds having excellent JNK protein kinase inhibitory action and satisfying requirements in, for example, pharmacological activities, dosage, and safety as pharmaceutical drugs have not yet been found.

Disclosure of the Invention

After intensive investigations under these circumstances, the present inventors have found novel

indazol compounds having JNK inhibitory action. That is, the present invention relates to:

<1> a compound represented by the following formula:



(I)

(wherein R^1 is a C_6-C_{14} aromatic cyclic hydrocarbon group which may be substituted or a 5- to 14-membered aromatic heterocyclic group which may be substituted;

R^2, R^4 and R^5 each independently represent a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a nitro group, a carboxyl group, a C_1-C_6 alkyl group which may be substituted, a C_1-C_6 alkoxy group which may be substituted, a C_2-C_7 acyl group which may be substituted, $-CO-NR^{2a}R^{2b}$, $-NR^{2b}CO-R^{2a}$ or $-NR^{2a}R^{2b}$ (wherein R^{2a} and R^{2b} each independently represent a hydrogen atom or a C_1-C_6 alkyl group which may be substituted), wherein at least one of R^2, R^4 and R^5 is not hydrogen;

L is a single bond, a C_1-C_6 alkylene group which may be substituted, a C_2-C_6 alkenylene group which may be substituted or a C_2-C_6 alkynylene group which may be substituted;

X is a group represented by $-CO-NR^8-V^2-$, NR^8-CO-V^2-,

or $-NR^8-SO_2-V^2-$ (wherein R^8 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_1-C_6 alkyl group which may be substituted, a C_2-C_6 alkenyl group which may be substituted, a C_2-C_6 alkynyl group which may be substituted, a C_1-C_6 alkoxy group which may be substituted, a C_2-C_6 alkenyloxy group which may be substituted, a C_1-C_6 alkylthio group which may be substituted, a C_2-C_6 alkenylthio group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_3-C_8 cycloalkenyl group which may be substituted, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted, a C_6-C_{14} aromatic cyclic hydrocarbon group which may be substituted or a 5- to 14-membered aromatic heterocyclic group which may be substituted; and V^2 is a single bond or a C_1-C_6 alkylene group which may be substituted); and

Y is a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, a cyano group, a carboxyl group, a C_1-C_6 alkyl group which may be substituted, a C_2-C_6 alkenyl group which may be substituted, a C_2-C_6 alkynyl group which may be substituted, a C_1-C_6 alkoxy group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_3-C_8 cycloalkenyl group which may be

substituted, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted, a C_6-C_{14} aromatic cyclic hydrocarbon group which may be substituted, a 5- to 14-membered aromatic heterocyclic group which may be substituted, an amino group or -W-R^{15} (wherein W is -CO- or -SO_2-; and R^{15} is a C_1-C_6 alkyl group which may be substituted, a C_6-C_{14} aromatic cyclic hydrocarbon group which may be substituted, a 5- to 14-membered aromatic heterocyclic group which may be substituted or an amino group)), a salt thereof or a hydrate of them;

<2> the compound according to the above <1>, a salt thereof or a hydrate of them, wherein R^2, R^4 and R^5 each independently represent a hydrogen atom, a halogen atom or a C_1-C_6 alkoxy group which may be substituted;

<3> the compound according to the above <1> or <2>, a salt thereof or a hydrate of them, wherein R^5 is a hydrogen atom;

<4> the compound according to any one of the above <1> to <3>, a salt thereof or a hydrate of them, wherein R^4 is a hydrogen atom;

<5> the compound according to any one of the above <1> to <4>, a salt thereof or a hydrate of them, wherein R^2 is a hydrogen atom;

<7> the compound according to any one of the above <1> to <6>, a salt thereof or a hydrate of them, wherein L is a single bond or a methylene group;

<8> the compound according to any one of the above <1> to <6>, a salt thereof or a hydrate of them, wherein L is a single bond;

<9> the compound according to any one of the above <1> to <8>, a salt thereof or a hydrate of them, wherein R^1 is a C_6-C_{14} aromatic cyclic hydrocarbon group or a 5- to 14-membered aromatic heterocyclic group; and R^1 is a group which may be substituted by one to three groups selected from the following Substituent Group "a":

<Substituent Group "a"> the group consisting of (1) (a) C_1-C_6 alkyl groups, (b) C_1-C_6 alkoxy groups, (c) C_1-C_7 acyl groups, (d) an amido group, (e) an amino group and (f) C_3-C_8 cycloalkyl groups, each of which may be substituted by one to three groups selected from the following Substituent Group "b", (2) halogen atoms, (3) a hydroxyl group, (4) a nitro group, (5) a cyano group, and (6) a carboxyl group;

<Substituent Group "b"> the group consisting of C_1-C_6 alkyl groups, halogen atoms, a hydroxyl group, a nitro group, a cyano group and a carboxyl group;

<10> the compound according to any one of the above <1> to <8>, a salt thereof or a hydrate of them, wherein R^1 is a phenyl group, a naphthyl group or a 5- to 10- aromatic heterocyclic group; and R^1 is a group which may be

substituted by one to three groups selected from the Substituent Group "a" as described in the above <9>;

<11> the compound according to any one of the above <1> to <8>, a salt thereof or a hydrate of them, wherein R^1 is a phenyl group, 2-naphthyl group, pyridyl group, 2-thienyl group, 2-furyl group, 2-benzofuryl group, 2-quinolyl group or 2-benzothienyl group; and R^1 is a group which may be substituted by one to three groups selected from the Substituent Group "a" described in the above <9>;

<12> the compound according to any one of the above <1> to <8>, a salt thereof or a hydrate of them, wherein R^1 is a 2-naphthyl group, 2-benzofuryl group or 2-benzothienyl group; and R^1 is a group which may be substituted by one to three groups selected from the Substituent Group "a" as described in the above <9>;

<13> the compound according to any one of the above <9> to <12>, a salt thereof or a hydrate of them, wherein the Substituent Group "a" is the group consisting of (1) C_1-C_6 alkyl groups which may be substituted by one to three groups selected from the group consisting of a halogen atom, a hydroxyl group and a cyano group, (2) C_1-C_6 alkoxy groups which may be substituted by one to three groups selected from the group consisting of a halogen atom, a hydroxyl group and a cyano group, (3) halogen atoms, (4) a hydroxyl group, and (5) a cyano group;

<14> the compound according to any one of the above <9> to

2002255263 23 Nov 2006

<12>, a salt thereof or a hydrate of them, wherein the Substituent Group "a" is halogen atoms;

<16> the compound according to the above <15>, a salt thereof or a hydrate of them, wherein R^8 is a hydrogen atom;

<17> the compound according to any one of the above <1> to <14>, a salt thereof or a hydrate of them, wherein X is a group represented by $-CC-NH-(CH_2)_t-$ (wherein t is 0 or 1);

<18> the compound according to any one of the above <1> to <14>, a salt thereof or a hydrate of them, wherein X is a group represented by $-NH-CO-(CH_2)_t-$ (wherein t is 0 or 1);

<19> the compound according to any one of the above <1> to <18>, a salt thereof or a hydrate of them, wherein Y is a C_1-C_6 alkyl group, a C_6-C_{14} aromatic cyclic hydrocarbon group, a C_1-C_6 alkoxy group, a C_3-C_8 cycloalkyl group, a 5- to 14-membered non-aromatic heterocyclic group and a 5- to 14-membered aromatic heterocyclic group, and Y is a group which may be substituted by one to three groups selected from the following Substituent Group "a2":

<Substituent Group "a2"> the group consisting of (1) (a) C_1-C_6 alkyl groups, (b) C_2-C_6 alkenyl groups, (c) C_2-C_6

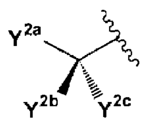
alkynyl groups, (d) C_1-C_6 alkoxy groups, (e) C_2-C_7 acyl groups, (f) an amide group, (g) an amino group, (h) a C_3-C_8 cycloalkyl group, (i) C_3-C_8 cycloalkenyl groups, (j) C_6-C_{14} aromatic cyclic hydrocarbon groups, (k) 5- to 14-membered aromatic heterocyclic groups, (l) C_6-C_{14} aryloxy groups, and (m) 5- to 14-membered non-aromatic heterocyclic groups, each of which may be substituted by one to three groups selected from the following <Substituent Group "b2">, (2) halogen atoms, (3) a hydroxyl group, (4) a nitro group, (5) a cyano group, and (6) a carboxyl group;

<Substituent Group "b2"> the group consisting of C_1-C_6 alkyl groups, halogen atoms, a hydroxyl group, a nitro group, a cyano group, and a carboxyl group;

<20> the compound according to any one of the above <1> to <18>, a salt thereof or a hydrate of them, wherein Y is a C_3-C_8 cycloalkyl group, a phenyl group, a 5- or 6-membered non-aromatic heterocyclic group or a 5- or 6-membered aromatic heterocyclic group, and Y is a group which may be substituted by one to three groups selected from the Substituent Group "a2" as described in the above <19>;

<21> the compound according to any one of the above <1> to <18>, a salt thereof or a hydrate of them, wherein Y is a furyl group, a thienyl group, a pyrrolyl group, a phenyl group, a pyridyl group, a C_3-C_8 cycloalkyl group, a tetrahydrofuran-yl group, a tetrahydrothiophenyl group, a pyrrolidinyl group, a tetrahydrofuran-2-one-yl group, a

pyrrolidin-2-one-yl group or a group represented by the formula:



(wherein Y^{2a} is a group represented by $-CONH_2$ or $-CH_2OH$; and Y^{2b} and Y^{2c} each independently represent a hydrogen atom, a phenyl group which may be substituted or a C_1-C_6 alkyl group which may be substituted), and wherein Y is a group which may be substituted by one to three groups selected from the Substituent Group "a2" as described in the above <19>;

<22> the compound according to any one of the above <1> to <18>, a salt thereof or a hydrate of them, wherein Y is a furyl group or a thienyl group; and Y is a group which may be substituted by one to three groups selected from the Substituent Group "a2" as described in the above <19>;

<23> the compound according to any one of the above <19> to <22>, a salt thereof or a hydrate of them, wherein the Substituent Group "a2" is the group consisting of (1) (a) C_1-C_6 alkyl groups, (b) C_1-C_6 alkoxy groups, (c) C_1-C_7 acyl groups, (d) an amide group, (e) an amino group, and (f) C_3-C_8 cycloalkyl groups, each of which may be substituted by one to three groups selected from the following <Substituent Group "b2">, (2) halogen atoms, (3) a hydroxyl group, (4) a nitro group, (5) a cyano group, and (6) a

carboxyl group, and the Substituent Group "b2" is the group consisting of C_1-C_6 alkyl groups, halogen atoms, a hydroxyl group, a nitro group, a cyano group, and a carboxyl group;

<24> the compound according to any one of the above <19> to <22>, a salt thereof or a hydrate of them, wherein the Substituent Group "a2" is the group consisting of (1) C_1-C_6 alkoxy groups, (2) halogen atoms, and (3) a cyano group;

<25> a c-Jun amino-terminal kinaase (JNK) inhibitor, comprising the compound according to the above <1>, a salt thereof or a hydrate of them.

<26> c-Jun amino-terminal kinaseamino-terminal kinase 1 (JNK 1), c-Jun amino-terminal kinaseamino-terminal kinase 2 (JNK 2) and/or c-Jun amino-terminal kinaseamino-terminal kinase 3 (JNK 3) inhibitors, comprising the compound according to the above <1>, a salt thereof or a hydrate of them;

<27> an agent for treating or preventing an immunological diseases or inflammatory diseases, comprising the compound according to the above <1>, a salt thereof or a hydrate of them;

<28> the agent for treating or preventing according to the above <27>, wherein the immunological diseases or inflammatory diseases is sepsis, chronic rheumatoid arthritis, osteoarthritis, gout, psoriasis, psoriatic arthritis, bronchitis, chronic obstructive lung disease, cystic fibrosis, insulin-dependent type I diabetes,

autoimmune thyroiditis, Crohn's disease, ulcerative colitis, atopic dermatitis, asthma, allergic rhinitis, hepatitis, systemic lupus erythematosus, acute and chronic graft rejection after organ transplantation, graft versus host diseases, eczema, urticaria, myasthenia gravis, acquired immunodeficiency syndrome, idiopathic thrombocytopenic purpura or glomerular nephritis;

<29> an agent for treating or preventing neurodegenerative diseases, comprising the compound according to the above <1>, a salt thereof or a hydrate of them;

<30> the agent for treating or preventing according to the above <29>, wherein the neurodegenerative diseases is acute neurodegenerative disease;

<31> the agent for treating or preventing according to the above <30>, wherein the acute neurodegenerative diseases is acute stage of cerebrovascular disorder, head injury, spinal code injury, or neuropathy due to hypoxia or hypoglycemia;

<32> the agent for treating or preventing according to the above <29>, wherein the neurodegenerative diseases is chronic neurodegenerative disease;

<33> an agent for treating or preventing Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis or spinocerebellar degeneration, which comprises the compound according to the above <1>, a salt thereof or a hydrate of

them;

<34> the agent for treating or preventing according to the above <29>, wherein the neurodegenerative disease is epilepsy, hepatic encephalopathy, peripheral neuropathy, Parkinsonian syndrome, L-DOPA-induced dyskinesia in treatment of Parkinson's disease, spastic pralysis, pain or neuralgi;

<35> the agent for treating or preventing according to the above <29>, wherein the neurodegenerative disease is infectious encephalomyelitis, cerebrovascular dementia, dementia or neurosis caused by meningitis;

<36> the agent for treating or preventing according to the above <35>, wherein the infectious encephalomyelitis is HIV encephalomyelitis;

<37> use of the compound according to the above <1>, a salt thereof or a hydrate of them, for therapy or prophylaxis of an immunological diseases, inflammatory diseases and/or neurodegenerative diseases;

<38> use of the compound according to the above <1>, a salt thereof or a hydrate of them, for producing an agent for treating an immunological diseases, inflammatory diseases and/or neurodegenerative diseases;

<39> use of the compound according to the above <1>, a salt thereof or a hydrate of them, for producing a c-Jun amino-terminal kinase 3 (JNK 3) inhibitor;

<40> a method for treating or preventing a disease against

which inhibition of c-Jun amino-terminal kinaseamino-terminal kinase 3 (JNK 3) is effective, an immunological disease, an inflammatory disease and/or a neurodegenerative disease, which comprises administering a pharmacologically effective amount of the compound according to the above <1>, a salt thereof or a hydrate of them to a patient, etc.

The present invention provides a pharmaceutical composition comprising the compound according to claim 1, a salt thereof or a hydrate of them, and a pharmacologically acceptable carrier. The present invention also provides use of the compound according to claim 1, a salt thereof or a hydrate of them, for producing an agent for treating or preventing a disease against which inhibition of a c-Jun amino-terminal kinaseamino-terminal kinase (JNK) is effective, an immunological disease, an inflammatory disease or a neurodegenerative disease. The present invention further provides a method for treating or preventing a disease against which inhibition of a c-Jun amino-terminal kinase (JNK) is effective, an immunological disease, an inflammatory disease or a neurodegenerative disease, which comprises administering a pharmacologically effective amount of the compound according to claim 1, a salt thereof or a hydrate of them to a patient.

The meanings of symbols, terms etc. as used in the present description will be described, and the present invention will be illustrated in detail below.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

The term "and/or" as used in the present description means and includes both the cases of "and" and "or".

The term "JNK" as used in the present description means an enzyme that phosphorylates the N-terminus region of a c-Jun protein and includes, for example, JNK 1, JNK 2, and JNK 3. Such JNKs include three types, JNK 1, JNK 2 and JNK 3. JNK 1 and JNK 2 are expressed in most of tissues, but JNK 3 is particularly highly expressed in the brain (Neuron, 14, 67, 1995; Neuron, 22, 667, 1999).

The term "neurodegenerative disease(s)" as used in the present description means all of diseases generally classified as neurodegenerative diseases in the field of medicine and includes, but is not specifically limited to, "acute neurodegenerative diseases", "chronic neurodegenerative diseases", epilepsy, hepatic encephalopathy, peripheral neuropathy, Parkinsonian syndrome, L-DOPA-induced dyskinesia in treatment of Parkinson's disease, spastic pralysis, pain, neuralgia, infectious encephalomyelitis, cerebrovascular dementia, and dementia or neurological symptom due to meningitidis. The "acute neurodegenerative diseases" include, for example, acute stage of cerebrovascular disorder (e.g., subarachnoid hemorrhage and cerebral infarction), head injury, spinal code injury, neuropathy due to hypoxia, and neuropathy due to hypoglycemia. The "chronic neurodegenerative diseases" include, for example, Alzheimer's disease, Parkinson's

disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, and spinocerebellar degeneration.

The term "immunologic disease(s)" or "inflammatory disease(s)" as used in the present description means all of diseases classified as immunologic diseases in the field of medicine, and examples thereof include, but are not limited to, sepsis, chronic rheumatoid arthritis, osteoarthritis, gout, psoriasis, psoriatic arthritis, bronchitis, chronic obstructive lung disease, cystic fibrosis, insulin-dependent type I diabetes, autoimmune thyroiditis, Crohn's disease, ulcerative colitis, atopic dermatitis, asthma, allergic rhinitis, hepatitis, systemic lupus erythematosus, acute and chronic graft rejection after organ transplantation, graft versus host diseases, eczema, urticaria, myasthenia gravis, acquired immunodeficiency syndrome, idiopathic thrombocytopenic purpura, and glomerular nephritis.

In the specification of the present invention, there is the case where the structural formula of a compound represents a definite isomer. However, the present invention includes isomers such as geometrical isomers, optical isomers based on asymmetric carbon, stereoisomers and tautomers and is not limited by the description of the formula illustrated for the sake of convenience. Accordingly, although it is possible that an asymmetric carbon atom is present in a molecule and accordingly that

optically active substance and racemic substance may be present, the present invention is not limited thereto but covers any of them. Further, crystal polymorphism may be present but, again, there is no limitation but any of single crystal form or a mixture will do. The compound (I) or its salt related to the present invention may be an anhydride or a hydrate, and either of them are included in the scope of claim for patent in the present invention. The metabolite which is generated by decomposing the compound (I) related to the present invention *in vivo*, and the prodrug of the compound (I) or its salt related to the present invention produce are also included in the scope of claim for patent in the present invention.

The salts or hydrates of the compounds of the present invention are preferably those pharmacologically acceptable.

The term "halogen atom(s)" as used in the present description includes, for example, a fluorine atom, chlorine atom, bromine atom, and iodine atom, preferably a fluorine atom and chlorine atom, and more preferably a fluorine atom.

The term "C_1-C_6 alkyl group(s)" as used in the present description means a linear or branched alkyl group containing 1 to 6 carbon atoms and includes, for example, methyl group, ethyl group, n-propyl group, iso-propyl group, n-butyl group, iso-butyl group, sec-butyl group, tert-butyl group, n-pentyl group, 1,1-dimethylpropyl group, 1,2-

dimethylpropyl group, 2,2-dimethylpropyl group, 1-ethylpropyl group, 2-ethylpropyl group, n-hexyl group, 1-methyl-2-ethylpropyl group, 1-ethyl-2-methylpropyl group, 1,1,2-trimethylpropyl group, 1-propylpropyl group, 1-methylbutyl group, 2-methylbutyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group, 2,2-dimethylbutyl group, 1,3-dimethylbutyl group, 2,3-dimethylbutyl group, 2-ethylbutyl group, 2-methylpentyl group, and 3-methylpentyl group. More preferred examples are methyl group, ethyl group, n-propyl group, iso-propyl group, n-butyl group, iso-butyl group, sec-butyl group, tert-butyl group, and n-pentyl group.

The term "C_2-C_6 alkenyl group(s)" as used in the present description means a linear or branched alkenyl group containing 2 to 6 carbon atoms and includes, for example, vinyl group, allyl group, 1-propenyl group, 2-propenyl group, isopropenyl group, 2-methyl-1-propenyl group, 3-methyl-1-propenyl group, 2-methyl-2-propenyl group, 3-methyl-2-propenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 1-pentenyl group, 1-hexenyl group, 1,3-hexadienyl group, and 1,6-hexadienyl group.

The term "C_2-C_6 alkynyl group(s)" as used in the present description means a linear or branched alkynyl group containing 2 to 6 carbon atoms and includes, for example, ethynyl group, 1-propynyl group, 2-propynyl group, 1-butynyl group, 2-butynyl group, 3-butynyl group, 3-

methyl-1-propynyl group, 1-ethynyl-2propynyl group, 2-methyl-3-propynyl group, 1-pentynyl group, 1-hexynyl group, 1,3-hexadiynyl group, and 1,6-hexadiynyl group.

The term "C_1-C_6 alkylene group(s)" as used in the present description means a divalent group derived from the above-defined "C_1-C_6 alkyl group" by removal of one hydrogen atom at an arbitrary position and includes, for example, methylene group, ethylene group, methylethylene group, propylene group, ethylethylene group, 1,1-dimethylethylene group, 1,2-dimethylethylene group, trimethylene group, 1-methyltrimethylene group, 1-ethyltrimethylene group, 2-methyltrimethylene group, 1,1-dimethyltrimethylene group, tetramethylene group, pentamethylene group, and hexamethylene group, of which methylene group and 1,2-ethylene group are preferred.

The term "C_2-C_6 alkenylene group(s)" as used in the present description means a divalent group derived from the above-defined "C_2-C_6 alkenyl group" by removal of one hydrogen atom and includes, for example, vinylene groups, propenylene groups, butenylene groups, pentenylene groups, and hexenylene groups. Preferred examples are vinylene groups, propenylene groups, butenylene groups, and pentenylene groups, of which vinylene groups, propenylene groups, and butenylene groups are more preferred. Among them, 1,2-vinylene group and 1,3-propenylene group are further more preferred.

The term "C_2-C_6 alkynylene group(s)" as used in the present description means a divalent group derived from the above-defined "C_2-C_6 alkynyl group" by removal of further one hydrogen atom and includes, for example, ethynylene group, propynylene groups, butynylene groups, pentynylene groups, and hexynylene groups. Preferred examples are ethynylene group, propynylene groups, butynylene groups, and pentynylene groups, of which ethynylene group, propynylene groups, and butynylene groups are more preferred. Among them, ethynylene group and propynylene groups are further more preferred, of which ethynylene group is most preferred.

The term "C_3-C_8 cycloalkyl group(s)" as used in the present description means three to eight aliphatic cyclic hydrocarbon groups and includes, for example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, and cyclooctyl group, of which cyclopropyl group and cyclobutyl group are preferred.

The term "C_3-C_8 cycloalkenyl group(s)" as used in the present description means a C_3-C_8 cycloalkenyl group comprising 3 to 8 carbon atoms and includes, for example, cyclopenten-3-yl, cyclohexen-1-yl, and cyclohexen-3-yl.

The term "C_1-C_6 alkoxy group(s)" as used in the present description means an oxy group combined with the above-defined "C_1-C_6 alkyl group" and includes, for example, methoxy group, ethoxy group, n-propoxy group, iso-propoxy

group, sec-propoxy group, n-butoxy group, iso-butoxy group, sec-butoxy group, tert-butoxy group, n-pentyloxy group, iso-pentyloxy group, sec-pentyloxy group, n-hexoxy group, iso-hexoxy group, 1,1-dimethylpropyloxy group, 1,2-dimethylpropoxy group, 2,2-dimethylpropyloxy group, 2-ethylpropoxy group, 1-methyl-2-ethylpropoxy group, 1-ethyl-2-methylpropoxy group, 1,1,2-trimethylpropoxy group, 1,1,2-trimethylpropoxy group, 1,1-dimethylbutoxy group, 1,2-dimethylbutoxy group, 2,2-dimethylbutoxy group, 2,3-dimethylbutyloxy group, 1,3-dimethylbutyloxy group, 2-ethylbutoxy group, 1,3-dimethylbutoxy group, 2-methylpentoxy group, 3-methylpentoxy group, and hexyloxy group. Among them, methoxy group, ethoxy group, n-propoxy group, iso-propoxy group, and sec-propoxy group are preferred, of which methoxy group and ethoxy group are more preferred.

The term "C_2-C_6 alkenyloxy group(s)" as used in the present description means an oxy group combined with the above-defined "C_2-C_6 alkenyl group".

The term "C_2-C_6 alkenylthio group(s)" as used in the present description means a thio group combined with the above-defined "C_2-C_6 alkenyl group".

The term "C_1-C_6 alkoxycarbonyl group(s)" as used in the present description means a carbonyl group combined with the above-defined "C_1-C_6 alkoxy group" and includes, for example, methoxycarbonyl group, ethoxycarbonyl group, n-

propoxycarbonyl group, i-propoxycarbonyl group, n-butoxycarbonyl group, i-butoxycarbonyl group, sec-butoxycarbonyl group, and t-butoxycarbonyl group.

The term "C_2-C_7 acyl group(s)" as used in the present description means a carbonyl group combined with the above-defined "C_1-C_6 alkyl group" and includes, for example, acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, isovaleryl group, and pivaloyl group.

The term "C_1-C_6 alkylcarbamoyl group(s)" as used in the present description includes, for example, methylcarbamoyl group, ethylcarbamoyl group, *n*-propylcarbamoyl group, *iso*-propylcarbamoyl group, *n*-butylcarbamoyl group, *iso*-butylcarbamoyl group, *sec*-butylcarbamoyl group, *tert*-butylcarbamoyl group, *n*-pentylcarbamoyl group, 1,1-dimethylpropylcarbamoyl group, 1,2-dimethylpropylcarbamoyl group, 2,2-dimethylpropylcarbamoyl group, 1-ethylpropylcarbamoyl group, 2-ethylpropylcarbamoyl group, n-hexylcarbamoyl group, 1-methyl-2-ethylpropylcarbamoyl group, 1-ethyl-2-methylpropylcarbamoyl group, 1,1,2-trimethylpropylcarbamoyl group, 1-propylpropylcarbamoyl group, 1-methylbutylcarbamoyl group, 2-methylbutylcarbamoyl group, 1,1-dimethylbutylcarbamoyl group, 1,2-dimethylbutylcarbamoyl group, 2,2-dimethylbutylcarbamoyl group, 1,3-dimethylbutylcarbamoyl group, 2,3-dimethylbutylcarbamoyl group, 2-ethylbutylcarbamoyl group, 2-methylpentylcarbamoyl group, and 3-metylpentylcarbamoyl

group.

The term "C_1-C_6 alkylcarbonyloxy group(s)" as used in the present description means an oxy group combined with the above-defined "C_2-C_7 acyl group" and includes, for example, methylcarbonyloxy group, ethylcarbonyloxy group, *n*-propylcarbonyloxy group, *iso*-propylcarbonyloxy group, *n*-butylcarbonyloxy group, *iso*-butylcarbonyloxy group, *sec*-butylcarbonyloxy group, *tert*-butylcarbonyloxy group, *n*-pentylcarbonyloxy group, 1,1-dimethylpropylcarbonyloxy group, 1,2-dimethylpropylcarbonyloxy group, 2,2-dimethylpropylcarbonyloxy group, 1-ethylpropylcarbonyloxy group, 2-ethylpropylcarbonyloxy group, n-hexylcarbonyloxy group, 1-methyl-2-ethylpropylcarbonyloxy group, 1-ethyl-2-methylpropylcarbonyloxy group, 1,1,2-trimethylpropylcarbonyloxy group, 1-propylpropylcarbonyloxy group, 1-methylbutylcarbonyloxy group, 2-methylbutylcarbonyloxy group, 1,1-dimethylbutylcarbonyloxy group, 1,2-dimethylbutylcarbonyloxy group, 2,2-dimethylbutylcarbonyloxy group, 1,3-dimethylbutylcarbonyloxy group, 2,3-dimethylbutylcarbonyloxy group, 2-ethylbutylcarbonyloxy group, 2-methylpentylcarbonyloxy group, and 3-metylpentylcarbonyloxy group.

The term "C_1-C_6 alkylsulfonyl group(s)" as used in the present description means a sulfonyl group combined with the above-defined "C_1-C_6 alkyl group" and includes, for

example, methylsulfonyl group, ethylsulfonyl group, *n*-propylsulfonyl group, *iso*-propylsulfonyl group, *n*-butylsulfonyl group, *iso*-butylsulfonyl group, *sec*-butylsulfonyl group, *tert*-butylsulfonyl group, *n*-pentylsulfonyl group, 1,1-dimethylpropylsulfonyl group, 1,2-dimethylpropylsulfonyl group, 2,2-dimethylpropylsulfonyl group, 1-ethylpropylsulfonyl group, 2-ethylpropylsulfonyl group, n-hexylsulfonyl group, 1-methyl-2-ethylpropylsulfonyl group, 1-ethyl-2-methylpropylsulfonyl group, 1,1,2-trimethylpropylsulfonyl group, 1-propylpropylsulfonyl group, 1-methylbutylsulfonyl group, 2-methylbutylsulfonyl group, 1,1-dimethylbutylsulfonyl group, 1,2-dimethylbutylsulfonyl group, 2,2-dimethylbutylsulfonyl group, 1,3-dimethylbutylsulfonyl group, 2,3-dimethylbutylsulfonyl group, 2-ethylbutylsulfonyl group, 2-methylpentylsulfonyl group, and 3-metylpentylsulfonyl group.

The term "C_1-C_6 alkylsulfenyl group(s)" as used in the present description means a sulfenyl group combined with the above-defined "C_1-C_6 alkyl group" and includes, for example, methylsulfenyl group, ethylsulfenyl group, *n*-propylsulfenyl group, *iso*-propylsulfenyl group, *n*-butylsulfenyl group, *iso*-butylsulfenyl group, *sec*-butylsulfenyl group, *tert*-butylsulfenyl group, *n*-pentylsulfenyl group, 1,1-dimethylpropylsulfenyl group, 1,2-dimethylpropylsulfenyl group, 2,2-

dimethylpropylsulfenyl group, 1-ethylpropylsulfenyl group, 2-ethylpropylsulfenyl group, n-hexylsulfenyl group, 1-methyl-2-ethylpropylsulfenyl group, 1-ethyl-2-methylpropylsulfenyl group, 1,1,2-trimethylpropylsulfenyl group, 1-propylpropylsulfenyl group, 1-methylbutylsulfenyl group, 2-methylbutylsulfenyl group, 1,1-dimethylbutylsulfenyl group, 1,2-dimethylbutylsulfenyl group, 2,2-dimethylbutylsulfenyl group, 1,3-dimethylbutylsulfenyl group, 2,3-dimethylbutylsulfenyl group, 2-ethylbutylsulfenyl group, 2-methylpentylsulfenyl group, and 3-metylpentylsulfenyl group.

The term "C_1-C_6 alkylthio group(s)" as used in the present description means a thio group combined with the above-defined "C_1-C_6 alkyl group" and includes, for example, methylthio group, ethylthio group, *n*-propylthio group, *iso*-propylthio group, *n*-butylthio group, *iso*-butylthio group, *sec*-butylthio group, *tert*-butylthio group, *n*-pentylthio group, 1,1-dimethylpropylthio group, 1,2-dimethylpropylthio group, 2,2-dimethylpropylthio group, 1-ethylpropylthio group, 2-ethylpropylthio group, n-hexylthio group, 1-methyl-2-ethylpropylthio group, 1-ethyl-2-methylpropylthio group, 1,1,2-trimethylpropylthio group, 1-propylpropylthio group, 1-methylbutylthio group, 2-methylbutylthio group, 1,1-dimethylbutylthio group, 1,2-dimethylbutylthio group, 2,2-dimethylbutylthio group, 1,3-dimethylbutylthio group, 2,3-dimethylbutylthio group, 2-ethylbutylthio group, 2-

methylpentylthio group, and 3-methylpentylthio group.

The term "C_6-C_{14} aromatic cyclic hydrocarbon group(s)" as used in the present description means an aromatic cyclic hydrocarbon group comprising 6 to 14 carbon atoms and includes monocyclic groups as well as bicyclic groups, tricyclic groups, and other condensed rings. Examples of these groups include phenyl group, indenyl groups, 1-naphthyl group, 2-naphthyl group, azulenyl groups, heptalenyl groups, biphenylyl groups, indacenyl groups, acenaphthylenyl groups, fluorenyl groups, phenalenyl groups, phenanthrenyl groups, anthracenyl groups, cyclopentacyclooctenyl groups, and benzocyclooctenyl groups. In the "C_6-C_{14} aromatic cyclic hydrocarbon group", phenyl group, 1-naphthyl group and 2-naphthyl group are preferred, and phenyl group, indenyl group and 2-naphthyl group are more preferred.

The term "C_6-C_{14} aryloxy group(s)" as used in the present description means an oxy group combined with the above-defined "C_6-C_{14} aromatic cyclic hydrocarbon group".

The term "5- to 14-membered aromatic heterocyclic group(s)" as used in the present description means a monocyclic, bicyclic, or tricyclic 5- to 14-membered heterocyclic group containing one or more hetero atoms selected from the group consisting of nitrogen atoms, sulfur atoms and oxygen atoms. Examples of the group include 1) nitrogen-containing aromatic heterocyclic groups

such as pyrrolyl group, pyridyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, triazolyl group, tetrazolyl group, benzotriazolyl group, pyrazolyl group, imidazolyl group, benzimidazolyl group, indolyl group, isoindolyl group, indolizinyl group, purinyl group, indazolyl group, quinolyl group, isoquinolyl group, quinoxalinyl group, quinazolinyl group, cinnolinyl group, quinolizinyl group, phthalazinyl group, naphthyridinyl group, pteridinyl group, imidazotriazinyl group, pyrazinopyridazinyl group, acridinyl group, phenanthridinyl group, carbazolyl group, perimidinyl group, phenanthrolinyl group, phenazinyl group, imidazopyridinyl group, imidazopyrimidinyl group, pyrazolopyridinyl group or pyrazolopyridinyl group; 2) sulfur-containing aromatic heterocyclic groups such as thienyl group or benzothienyl group; 3) oxygen-containing aromatic heterocyclic groups such as furyl group, pyranyl group, benzofuryl group or isobenzofuryl group; and 4) aromatic heterocyclic groups each containing two or more different hetero atoms, such as thiazolyl group, isothiazolyl group, benzothiazolyl group, benzthiadiazolyl group, phenothiazinyl group, isoxazoly group, furazanyl group, phenoxazinyl group, oxazolyl group, isoxazolyl group, benzoxazolyl group, oxadiazolyl group, pyrazoloxazolyl group, imidazothiazolyl group, thienofuranyl group, furopyrrolyl group or pyridooxazinyl group.

The term "5- to 14-membered non-aromatic heterocyclic group(s)" as used in the present description means a non-aromatic heterocyclic group 1) which comprises 5 to 14 atoms,

2) which contains one or more hetero atoms as the atoms constituting the ring,

3) which may contain one to three carbonyl groups, and

4) which is a monocyclic, bicyclic or tricyclic ring.

Examples of the group include pyrrolidyl group, piperidyl group, piperazyl group, imidazolyl group, pyrazolidyl group, imidazolidyl group, morpholinyl group, tetrahydrofuryl group, tetrahydropyranyl group, aziridinyl group, oxiranyl group, and oxathiolanyl group. The non-aromatic heterocyclic group includes groups derived from a pyridone ring and non-aromatic condensed rings such as groups derived from phthalimide ring, or succinimide ring. Preferred examples of these groups are pyrrolidyl group, piperidyl group, piperazyl group, imidazolyl group, pyrazolidyl group, imidazolidyl group, morpholyl group, tetrahydrofuryl group, tetrahydropyranyl group, aziridinyl group, oxiranyl group, and oxathiolanyl group.

The term "5- to 10-membered aromatic heterocyclic group(s)" as used in the present description means a monocyclic or bicyclic aromatic heterocyclic group, whose ring comprises 5 to 10 atoms including one or more hetero

atoms.

Examples of the group include 1) nitrogen-containing aromatic heterocyclic groups such as pyrrolyl group, pyridyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, triazolyl group, tetrazolyl group, benzotriazolyl group, pyrazolyl group, imidazolyl group, benzimidazolyl group, indolyl group, isoindolyl group, indolizinyl group, purinyl group, indazolyl group, quinolyl group, isoquinolyl group, quinolidyl group, phthalazyl group, naphthyridinyl group, quinoxalyl group, quinazolinyl group, cinnolinyl group, pteridinyl group, imidazotriazinyl group, pyrazinopyridazinyl group, imidazopyridinyl group, imidazopyrimidinyl group, pyrazolopyridinyl group or pyrazolopyridinyl group; 2) sulfur-containing aromatic heterocyclic groups such as thienyl group or benzothienyl group; 3) oxygen-containing aromatic heterocyclic groups such as furyl group, pyranyl group, benzofuryl group or isobenzofuryl group; and 4) aromatic heterocyclic groups each containing two or more different hetero atoms, such as thiazolyl group, isothiazolyl group, benzothiazolyl group, benzthiadiazolyl, isoxazoly group, furazanyl group, oxazolyl group, isoxazolyl group, benzoxazolyl group, oxadiazolyl group, pyrazoloxazolyl group, imidazothiazolyl group, thienofuranyl group, furopyrrolyl group or pyridooxazinyl group.

Preferred examples of the group are pyrrolyl group,

furyl group, thienyl group, pyridyl group, benzothienyl group, benzofuryl group, indolyl group, and indazolyl group, of which furyl group, thienyl group, benzothienyl group and benzofuryl group are more preferred.

The term "5- or 6-membered aromatic heterocyclic group(s)" as used in the present description means a monocyclic aromatic heterocyclic group, whose ring comprises 5 or 6 atoms including one or more hetero atoms. Examples of the group include pyrrolyl group, imidazolyl group, pyrazolyl group, 1,2,3-triazolyl group, pyridyl group, pyridazyl group, pyrimidinyl group, pyrazinyl group, furyl group, thienyl group, thiazolyl group, oxazolyl group, and isoxazolyl group, of which pyrrolyl group, pyridyl group, furyl group and thienyl group are preferred. Among them, furyl group and thienyl group are more preferred.

The term "5- or 6-membered non-aromatic heterocyclic group(s)" as used in the present description means a 5- or 6-membered heterocyclic group containing one or more hetero atoms selected from the group consisting of nitrogen atoms, sulfur atoms and oxygen atoms. Examples of the group include piperidyl group, piperazyl group, morpholyl group, thiomorpholyl group, tetrahydro-2-pyron-yl group, tetrahydropyran-yl groups, tetrahydrothiopyran-yl groups, piperidin-2-one-yl groups, tetrahydrofuran-yl group, tetrahydrothiophen-yl group, pyrrolidinyl group, tetrahydrofuran-2-one-yl groups, and pyrrolidin-2-one-yl

groups. Preferred examples of the "5- or 6-membered nonaromatic heterocyclic group" are piperidyl group, piperazyl group, morpholyl group, thiomorpholyl group, tetrahydro-2-pyron-yl groups, tetrahydropyran-yl groups, tetrahydrothiopyran-yl groups, and piperidin-2-one-yl groups.

The term "5-membered non-aromatic heterocyclic group(s)" as used in the present description means a 5-membered heterocyclic group containing one or more hetero atoms selected from the group consisting of nitrogen atoms, sulfur atoms, and oxygen atoms and concretely means, for example, tetrahydrofuran-yl group, tetrahydrothiophen-yl group, pyrrolidinyl group, tetrahydrofuran-2-one-yl groups, or pyrrolidin-2-one-yl groups.

The term "amino group(s)" as used in the present description means a group represented by the formula $-NH_2$.

The term "amide group(s)" as used in the present description means a group represented by the formula $-CO-NH_2$.

The term "furyl group" as used in the present description means 2-furyl group or 3-furyl group, of which 2-furyl group is preferred.

The term "thienyl group" as used in the present description means 2-thienyl group or 3-thienyl group, of which 2-thienyl group is preferred.

The term "pyrrolyl group" as used in the present

description means 1-pyrrolyl group, 2-pyrrolyl group, or 3-pyrrolyl group, of which 2-pyrrolyl group is preferred.

The term "tetrahydrofuran-yl group" as used in the present description means tetrahydrofuran-2-yl group or tetrahydrofuran-3-yl group, of which tetrahydrofuran-2-yl group is preferred.

The term "tetrahydrothiophen -yl group" as used in the present description means tetrahydrothiophen-2-yl group or tetrahydrothiophen-3-yl group, of which tetrahydrothiophen-2-yl group is preferred.

The term "pyrrolidinyl group" as used in the present description means 1-pyrrolidinyl group, 2-pyrrolidinyl group, or 3-pyrrolidinyl group, of which 2-pyrrolidinyl group is preferred.

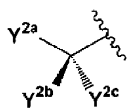
The term "tetrahydrofuran-2-one-yl group" as used in the present description means tetrahydrofuran-2-one-3-yl group, tetrahydrofuran-2-one-4-yl group, or tetrahydrofuran-2-one-5-yl group, of which tetrahydrofuran-2-one-5-yl group is preferred.

The term "pyrrolidin-2-one-yl group" as used in the present description means pyrrolidin-2-one-1-yl group, pyrrolidin-2-one-3-yl group, pyrrolidin-2-one-4-yl group, or pyrrolidin-2-one-5-yl group, of which pyrrolidin-2-one-5-yl group is preferred.

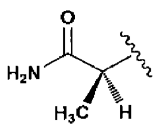
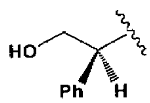
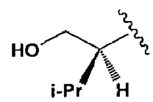
The term "quinolyl group" as used in the present description means a monovalent group derived from a

quinoline ring by removal of any one hydrogen atom and includes, for example, 2-quinolyl group, 3-quinolyl group, 4-quinolyl group, 5-quinolyl group, 6-quinolyl group, 7-quinolyl group, and 8-quinolyl group, of which 2-quinolyl group is preferred.

Preferred examples of the group represented by the formula:



(wherein Y^{2a}, Y^{2b} and Y^{2c} have the same meanings as defined above) are groups represented by the following formulae:

  or 

The term "may be substituted" as used in the present description has the same meaning as in "may have one or plural substituents in an arbitrary combination at position(s) that can be substituted".

Typical examples of the substituent in the term "may be substituted" as used in the present description include:

(1) halogen atoms (e.g., fluorine atom, chlorine atom, bromine atom, and iodine atom);

(2) hydroxyl group;

(3) cyano group;

(4) nitro group;

(5) carboxyl group;

(6) amino group;

(7) C_1-C_6 alkyl groups (e.g., methyl group, ethyl group, n-propyl group, iso-propyl group, n-butyl group, tert-butyl group, n-pentyl group, 1,1-dimethylpropyl group, 1,2-dimethylpropyl group, 2,2-dimethylpropyl group, 1-ethylpropyl group, 2-ethylpropyl group, and n-hexyl group);

(8) C_2-C_6 alkenyl groups (e.g., vinyl group, allyl group, 1-propenyl group, 2-propenyl group, isopropenyl group, 2-methyl-1-propenyl group, and 3-methyl-1-propenyl group);

(9) C_2-C_6 alkynyl groups (e.g., ethynyl group, 1-propynyl group, 2-propynyl group, 1-butynyl group, 2-butynyl group, 3-butynyl group, 3-methyl-1-propynyl group, 1-ethynyl-2propynyl group, and 2-methyl-3-propynyl group);

(10) C_3-C_8 cycloalkyl groups (e.g., cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, and cyclooctyl group);

(11) C_3-C_8 cycloalkenyl groups (e.g., cyclopropen-1-yl, cyclopropen-3-yl, cyclobuten-1-yl, cyclobuten-3-yl, 1,3-cyclobutadien-1-yl, cyclopenten-1-yl, cyclopenten-3-yl, cyclopenten-4-yl, 1,3-cyclopentadien-1-yl, 1,3-cyclopentadien-2-yl, 1,3-cyclopentadien-5-yl, cyclohexen-1-yl, cyclohexen-3-yl, cyclohexen-4-yl, 1,3-cyclohexadien-1-yl, 1,3-cyclohexadien-2-yl, 1,3-cyclohexadien-5-yl, 1,4-cyclohexadien-3-yl, and 1,4-cyclohexadien-1-yl);

(12) C_1-C_6 alkoxy groups (e.g., methoxy group, ethoxy group,

n-propoxy group, iso-propoxy group, sec-propoxy group, n-butoxy group, iso-butoxy group, sec-butoxy group, tert-butoxy group, n-pentyloxy group, iso-pentyloxy group, sec-pentyloxy group, n-hexoxy group, iso-hexoxy group, 1,1-dimethylpropyloxy group, 1,2-dimethylpropoxy group, and 2,2-dimethylpropyloxy group);

(13) C_1-C_6 alkenyloxy groups (e.g., vinyloxy group, allyloxy group, 1-propenyloxy group, 2-propenyloxy group, isopropenyloxy group, 2-methyl-1-propenyloxy group, 3-methyl-1-propenyloxy group, 2-methyl-2-propenyloxy group, 3-methyl-2-propenyloxy group, 1-butenyloxy group, 2-butenyloxy group, 3-butenyloxy group, 1-pentenyloxy group, 1-hexenyloxy group, 1,3-hexadienyloxy group, and 1,6-hexadienyloxy group);

(14) C_1-C_6 alkylthio groups (e.g., methylthio group, ethylthio group, n-propylthio group, iso-propylthio group, n-butylthio group, iso-butylthio group, sec-butylthio group, tert-butylthio group, n-pentylthio group, 1,1-dimethylpropylthio group, 1,2-dimethylpropylthio group, 2,2-dimethylpropylthio group, 1-ethylpropylthio group, 2-ethylpropylthio group, n-hexylthio group, and 1-methyl-2-ethylpropylthio group);

(15) C_1-C_6 alkenylthio groups (e.g., vinylthio group, allylthio group, 1-propenylthio group, 2-propenylthio group, isopropenylthio group, 2-methyl-1-propenylthio group, 3-methyl-1-propenylthio group, 2-methyl-2-propenylthio group,

3-methyl-2-propenylthio group, 1-butenylthio group, 2-butenylthio group, 3-butenylthio group, 1-pentenylthio group, 1-hexenylthio group, 1,3-hexadienylthio group, and 1,6-hexadienylthio group);

(16) C_1-C_{14} aryloxy groups (e.g., phenyloxy group);

(17) C_2-C_7 acyl groups (e.g., acetyl group, propionyl group, and butyroyl group);

(18) C_6-C_{14} aromatic cyclic hydrocarbon groups (e.g., phenyl group, 1-naphthyl group, and 2-naphthyl group);

(19) 5- to 14-membered non-aromatic heterocyclic groups (e.g., 1) pyrrolidyl group, piperidyl group, piperazyl group, imidazolyl group, pyrazolidyl group, imidazolidyl group, morpholyl group, tetrahydrofuryl group, tetrahydropyranyl group, aziridinyl group, oxiranyl group, and oxathiolanyl group;

2) groups derived from a pyridone ring; and

3) groups derived from condensed rings such as phthalimide ring and succinimide ring);

(20) 5- to 14-membered aromatic heterocyclic groups (e.g., pyrrolyl group, pyridyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, imidazolyl group, benzimidazolyl group, indolyl group, indazolyl group, quinolyl group, isoquinolyl group, thienyl group, benzothienyl group, furyl group, pyranyl group, benzofuryl group, thiazolyl group, and benzothiazolyl group);

(21) amide group;

(22) sulfonyl groups each having a C_1-C_6 aliphatic hydrocarbon group as a substituent;

(23) sulfonamide group;

(24) C_1-C_6 alkyl-carbamoyl groups;

(25) C_1-C_6 alkoxy-carbonyl groups;

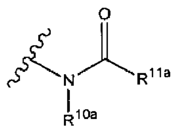
(26) C_1-C_6 alkyl-carbonyloxy groups;

(27) C_1-C_6 alkylsulfonyl groups;

(28) C_1-C_6 alkylsulfinyl groups;

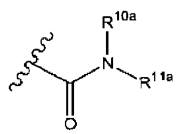
(29) formyl group;

(30) groups represented by the following formula:



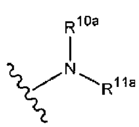
wherein R^{10a} and R^{11a} each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

(31) groups represented by the following formula:



wherein R^{10a} and R^{11a} each independently represent a hydrogen atom or a C_1-C_6 alkyl group; and

(32) groups represented by the following formula:



wherein R^{10a} and R^{11a} each independently represent a hydrogen

42

atom or a C_1-C_6 alkyl group. The term "may be substituted" as used in the present description means that may have one to four substituents selected from the group consisting of these substituents.

Further, in the aforementioned substituents (6) to (23) as the substituent in "may be substituted", the amino group, C_1-C_6 alkyl groups, C_2-C_6 alkenyl groups, C_2-C_6 alkynyl groups, C_3-C_8 cycloalkyl groups, C_3-C_8 cycloalkenyl groups, C_1-C_6 alkoxy groups, C_2-C_6 alkenyloxy groups, C_1-C_6 alkylthio groups, C_2-C_6 alkenylthio groups, C_6-C_{14} aryloxy groups, C_2-C_7 acyl groups, C_6-C_{14} aromatic cyclic hydrocarbon groups, 5- to 14-membered non-aromatic cyclic hydrocarbon groups or 5- to 14-membered aromatic heterocyclic groups, amide group, sulfonyl groups each having a C_1-C_6 aliphatic hydrocarbon group as a substituent, or sulfonamide group may be further substituted by one to four groups selected from the group consisting of:

(a) halogen atoms,

(b) hydroxyl group,

(c) cyano group,

(d) nitro group,

(e) carboxyl group,

(f) amino group,

(g) C_1-C_6 alkyl groups,

(h) C_2-C_6 alkenyl groups,

(i) C_2-C_6 alkynyl groups,

(j) C_3-C_8 cycloalkyl groups,

(k) C_3-C_8 cycloalkenyl groups,

(l) C_1-C_6 alkoxy groups,

(m) C_2-C_6 alkenyloxy groups,

(n) C_1-C_6 alkylthio groups,

(o) C_2-C_6 alkenylthio groups,

(p) C_6-C_{14} aryloxy groups,

(q) C_2-C_7 acyl groups,

(r) C_6-C_{14} aromatic cyclic hydrocarbon groups,

(s) 5- to 14-membered non-aromatic cyclic hydrocarbon groups,

(t) 5- to 14-membered aromatic heterocyclic groups,

(u) amido group,

(v) sulfonyl groups each having a C_1-C_6 aliphatic hydrocarbon group as a substituent, and

(w) sulfonamido group described in (1) to (23).

Preferred examples of the substituent in the term "may be substituted" as used in the present description include:

(a-1) halogen atoms,

(a-2) hydroxyl group,

(a-3) nitrile group,

(a-4) C_1-C_6 alkyl groups, C_2-C_6 alkenyl groups, C_2-C_6 alkynyl groups, C_3-C_8 cycloalkyl groups and C_1-C_6 alkoxy groups, each of which may be substituted by one to three halogen atoms or hydroxyl groups,

(a-5) C_6-C_{10} aromatic cyclic hydrocarbon groups,

(a-6) 5- to 14-membered aromatic heterocyclic groups,

(a-7) 5- to 14-membered heterocyclic groups,

(a-8) carboxyl group,

(a-9) trifluoromethyl group,

(a-10) C_1-C_6 alkylcarbamoyl groups,

(a-11) C_1-C_6 akoxycarbonyl groups,

(a-12) C_2-C_7 acyl groups,

(a-13) C_1-C_6 alkylcarbonyloxy groups,

(a-14) C_1-C_6 alkylsulfonyl groups,

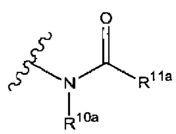
(a-15) C_1-C_6 alkylsulfinyl groups,

(a-16) C_1-C_6 alkylthio groups,

(a-17) nitro group,

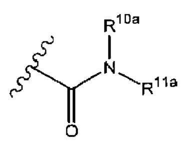
(a-18) formyl group,

(a-19) groups represented by the formula:



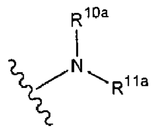
wherein R^{10a} and R^{11a} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, and

(a-20) groups represented by the formula:



wherein R^{10a} and R^{11a} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, and

(a-21) groups represented by the formula:



wherein R^{10a} and R^{11a} each independently represent a hydrogen atom or a C_1-C_6 alkyl group.

More preferred examples of the substituent in the term "may be substituted" as used in the present description include:

(a-1) halogen atoms,

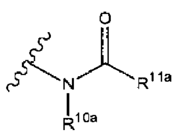
(a-2) hydroxyl group,

(a-3) nitrile group,

(a-4) C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups or C_1-C_6 alkoxy groups, each of which may be substituted by one to three halogen atoms or hydroxyl groups,

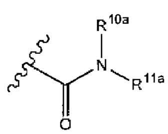
(a-17) nitro group,

(a-19) groups represented by the formula:



wherein R^{10a} and R^{11a} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, and

(a-20) groups represented by the formula:



46

wherein R^{10a} and R^{11a} each independently represent a hydrogen atom or a C_1-C_6 alkyl group.

Still more preferred examples of the substituent in the term "may be substituted" as used in the present description include halogen atoms, nitrile group, C_1-C_6 alkyl groups, C_3-C_8 cycloalkyl groups, C_1-C_6 alkoxy groups, and trifluoromethyl group.

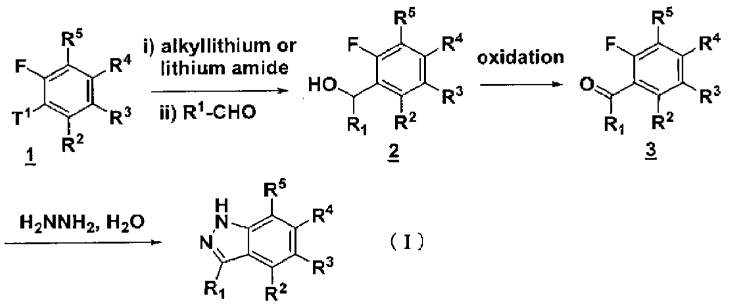
Further more preferred examples of the substituent in the term "may be substituted" as used in the present description include fluorine atom, cyclopropyl group, trifluoromethyl group, and methoxy group.

General Synthesis method

Typical production processes of the 1H-indazole compounds represented by the formula (I) according to the present invention will be illustrated below. In reaction schemes of the following Production Processes 1 to 40, R is a C_1-C_8 alkyl group; R^1, R^2, R^4, and R^5 have the same meanings as defined above; R^3 is a group represented by the formula -L-X-Y (wherein L, X and Y have the same meanings as the above-defined L, X and Y); T^1 is a hydrogen atom, a bromine atom or an iodine atom; T^2 is a halogen atom; T^3 is a sulfonate or a halogen atom; T^4 is a hetero atom (oxygen atom, nitrogen atom or sulfur atom); "Pro" represents a protecting group; Q is a C_1-C_8 alkyl group; Q^1, Q^2 and Q^3 each independently represent a C_1-C_8 alkyl group, or Q^1 and

Q^2 may be combined to form a ring; Q^4 and Q^5 each independently represent a group represented by the formula -Y (wherein Y has the same meaning as defined above); R^{1a} is a group represented by the formula R^1 (wherein R^1 has the same meaning as defined above); R^{19} has the same meaning as the above-defined group represented by R^2, R^4 or R^5; and p is an integer of 0, 1, 2, or 3.

Production Process 1



(I)

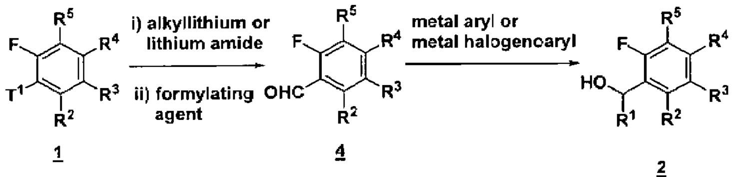
The compound (I) can be produced by treating the fluorobenzene 1 with, for example, an alkyllithium or lithium amide to thereby yield a metal aryl, allowing the metal aryl to react with an arylaldehyde to thereby yield the alcohol 2, oxidizing the alcohol 2 into the ketone 3, and then closing the indazole ring with hydrazine. The alkyllithium for converting the fluorobenzene 1 to the metal aryl includes, for example, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, and phenyllithium. Where necessary, an additive such as N,N,N',N'-tetramethylethylenediamine and hexamethylphosphoramide can

48

be added. The lithium amide includes, for example, lithium diisopropylamide, and lithium 2,2,6,6-tetramethylpiperidide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and preferred examples thereof are ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene and toluene. A reaction temperature is from -78°C to room temperature. Oxidizing agents for oxidizing the alcohol compound 2 include, for example, manganese dioxide, sulfur trioxide-pyridine complex, N-methylmorpholine-N-oxide, and chromic acid oxidizing agents. The oxidation can also be performed by Swern oxidation or Moffat oxidation. Solvents for use herein can be any solvents that are not involved in the reaction and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from -78°C to the reflux temperature of the solvent. The reaction for cyclization of the compound 3 with hydrazine monohydrate can be performed in the absence of, or in the presence of, a solvent. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, alcohol solvents such as methanol, ethanol or propanol, as well as

pyridine, dimethyl sulfoxide, benzene, and toluene. The amount of the hydrazine monohydrate is from 2 to 20 equivalents to the raw material. A reaction temperature is generally from 0°C to the reflux temperature of the solvent.

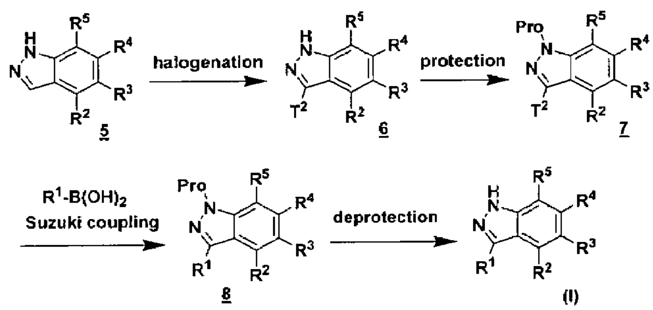
Production Process 2



The compound 2 can also be produced by Production Process 2. Initially, the fluorobenzene 1 is converted into to a metal aryl by the procedure of Production Process 1, and the metal aryl is allowed to react with a formylation agent to yield the compound 4. The formylation agent includes, for example, dimethylformamide, N-formylpiperidine, and methylphenylformamide. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene and toluene. A reaction temperature is from -78°C to room temperature. The compound 2 can be produced by allowing the compound 4 to react with a metal aryl or metal halogenoaryl. The metal aryl or metal halogenoaryl can be easily prepared, for example, by treating a halogenoaryl

using an alkyllithium, magnesium or zinc into an aryllithium or metal halogenoaryl. The alkyllithium includes, for example, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, and phenyllithium. Where necessary, an additive such as N,N,N',N'-tetramethylethylenediamine and hexamethylphosphoramide can be added. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene and toluene. A reaction temperature is from -78°C to room temperature.

Production Process 3



The compound (I) can also be produced by halogenating the 3-position of the indazole compound 5 to yield the compound 6, protecting the 1-position of the compound 6 to yield the compound 7, subjecting the compound 7 to Suzuki coupling with an arylboronic acid to yield the compound 8, and deprotecting the 1-position of the compound 8.

51

Reagents for halogenating the 3-position include, for example, *N*-bromosuccinimide, *N*-iodosuccinimide, *N*-chlorosuccinimide, and bromine. Where necessary, a radical reaction initiator such as 2,2'-azobisisobutyronitrile and benzoyl peroxide can be added. The amount of the halogenation reagent is from 1.05 to 1.2 equivalents to the raw material. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated hydrocarbons such as dichloromethane, chloroform or carbon tetrachloride, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from room temperature to the reflux temperature of the solvent.

Protecting groups for the 1-position include, for example, *tert*-butyloxycarbonyl group, *p*-toluenesulfonyl group, triphenylmethyl group, and methoxymethyl group. The *tert*-butyloxycarbonyl group or *p*-toluenesulfonyl group can be introduced by allowing the compound 6 to react with di-tert-butyl dicarbonate or p-toluenesulfonyl chloride in the presence of a base. Such bases are not specifically limited but preferred examples are triethylamine and 4-*N,N*-dimethylaminopyridine. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane,

halogenated hydrocarbons scuh as dichloromethane or chloroform, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from 0°C to the reflux temperature of the solvent.

The triphenylmethyl group or methoxymethyl group can be introduced by allowing the compound 6 to react with chlorotriphenylmethane or chloromethyl methyl ether in the presence of a base. Such bases are not specifically limited, but preferred examples are sodium hydride, potassium *tert*-butoxide, lithium diisopropylamide, potassium carbonate, and sodium hydroxide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from -20°C to the reflux temperature of the solvent.

Among arylboronic acids for use in Suzuki coupling, those commercially available will be purchased, and those not commercially available can be easily prepared according to a conventional procedure. Such an arylboronic acid can be prepared, for example, by treating a halogenoaryl with an alkyllithium, magnesium or zinc to convert the same into an aryllithium or a metal halogenoaryl, allowing the

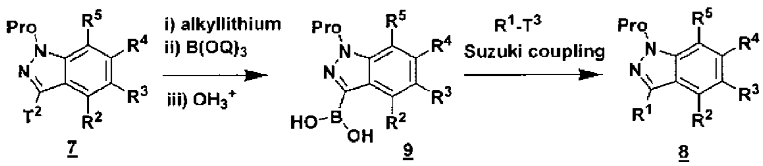
aryllithium or metal halogenoaryl to react with trialkyl-borate into a boric ester, and hydrolyzing the boric ester. The alkyllithium includes, for example, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, and phenyllithium. Where necessary, an additive such as N,N,N′,N′-tetramethylethylenediamine, and hexamethylphosphoramide can be added. The boric ester formed as a result of the reaction between the aryllithium and the trialkyl-boric acid can be hydrolyzed by adding water or by using an acid such as hydrochloric acid or sulfuric acid. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, of which ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane are preferred. A reaction temperature is from -78°C to room temperature. The amount of the arylboronic acid for use in Suzuki coupling is from 1 to 3 equivalents to the raw material. Catalysts for use herein include, for example, palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), and tetrakis(triphenylphosphine)palladium(0). The amount of the catalyst is about 5% by mole relative to the raw material. Where necessary, a phosphine ligand in an amount of two times by mole that of the catalyst can be added. Such phosphine ligands include, for example, tri-*tert*-butylphosphine, 2-(di-*tert*-butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, and triphenylphosphine.

Examples of bases for use herein are sodium hydrogencarbonate, sodium carbonate, potassium carbonate, cesium carbonate, and potassium fluoride. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, dimethylformamide, *N*-methylpyrrolidone, tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, and toluene. A reaction temperature is generally from room temperature to the reflux temperature of the solvent.

The *tert*-butyloxycarbonyl group and triphenylmethyl group can be easily deprotected (removed) by using an acid. Such acids include, for example, hydrochloric acid, sulfuric acid, and trifluoroacetic acid. Where necessary, a radical scavenger such as thiophenol or tri-*iso*-propylsilane can be added. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, alcohol solvents such as methanol or ethanol, and anisole. A reaction temperature is from -20°C to the reflux temperature of the solvent. The *tert*-butyloxycarbonyl group and p-toluenesulfonyl group can also be easily deprotected by using a base. Such bases include, but are not specifically limited to, aqueous sodium hydroxide and aqueous potassium hydroxide. Solvents for use herein are not specifically limited, as long as they are inert to the

reaction, and include, for example, alcohol solvents such as methanol or ethanol, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane. A reaction temperature is room temperature to the reflux temperature of the solvent. The methoxymethyl group can be deprotected by treating the compound with an acid and treating the residual aminal with aqueous ammonia.

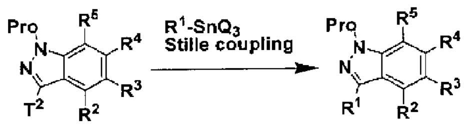
Production Process 4



The compound 8 can also be obtained by converting the compound 7 into the boronic acid 9 and subjecting the boronic acid 9 to Suzuki coupling with an aryl halide or aryl sulfonate. The boronic acid 9 can be obtained by converting the compound 7 into an aryllithium, allowing the aryllithium to react with trialkyl-borate to yield a boric ester, and hydrolyzing the boric ester. The alkyllithium for converting the compound 7 into an aryllithium includes, for example, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, and phenyllithium. Where necessary, an additive such as N,N,N',N'-tetramethylethylenediamine and hexamethylphosphoramide can be added. The boric ester formed as a result of the reaction between the aryllithium and the trialkyl borate can be hydrolyzed by adding water

or by using an acid such as hydrochloric acid or sulfuric acid. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, of which ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane are preferred. A reaction temperature is from -78°C to room temperature. The compound 8 can be produced by subjecting the boronic acid 9 and an aryl halide or aryl sulfonate to Suzuki coupling under the conditions of Production Process 3.

Production Process 5



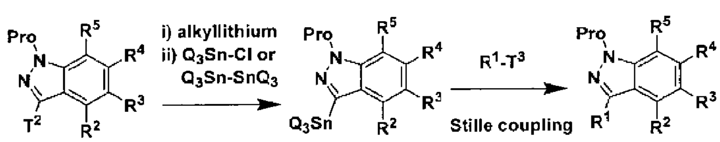
7 8

The compound 8 can also be produced by Stille coupling as shown in Production Process 5. Among aryltrialkyltins for use in Stille coupling, those commercially available will be purchased and those not commercially available can be easily prepared. Such an aryltrialkyltin can be prepared, for example, by treating a halogenoaryl with an alkyllithium, magnesium, or zinc to thereby yield an aryllithium or metal halogenoaryl, and allowing the aryllithium or metal halogenoaryl to react with a chlorotrialkyltin or hexaalkylditin. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, of which ether solvents such as

57

diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane are preferred. A reaction temperature is from -78°C to room temperature. The amount of the aryltrialkyltin for use in Stille coupling is from 1 to 3 equivalents to the raw material. Catalysts for use herein include, for example, palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), and tetrakis(triphenylphosphine)palladium(0). The amount of the catalyst is about 5% by mole relative to the raw material. Where necessary, a phosphine ligand in an amount of two times by mole that of the catalyst can be added. Such phosphine ligands include, for example, tri-*tert*-butylphosphine, 2-(di-*tert*-butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, and triphenylphosphine. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, dimethylformamide, *N*-methylpyrrolidone, tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, toluene, and xylenes. A reaction temperature is generally from room temperature to the reflux temperature of the solvent.

Production Process 6

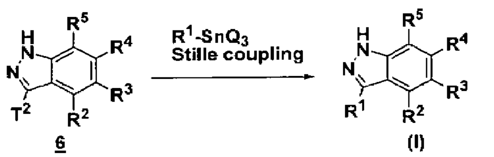


7　　10　　8

58

The compound 8 can also be obtained by converting the compound 7 into the tin compound 10, and subjecting the tin compound 10 to Stille coupling with an aryl halide or aryl sulfonate. The tin compound 10 can be obtained by converting the compound 7 into an aryllithium under the same conditions as in Production Process 4, and allowing the aryllithium to react with a chlorotrialkyltin or hexaalkylditin. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, of which ether solvents diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane are preferred. A reaction temperature is from -78°C to room temperature. The compound 8 can be produced by subjecting the tin compound 10 and an aryl halide or aryl sulfonate to Stille coupling under conditions of Production Process 5.

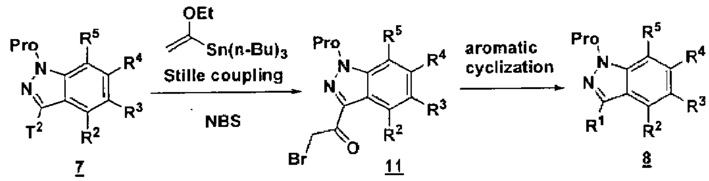
Production Process 7



The compound (I) can also be produced by subjecting the compound 6 in which the 1-position is not protected to Stille coupling under conditions of Production Process 5, as shown in Production Process 7.

Production Process 8

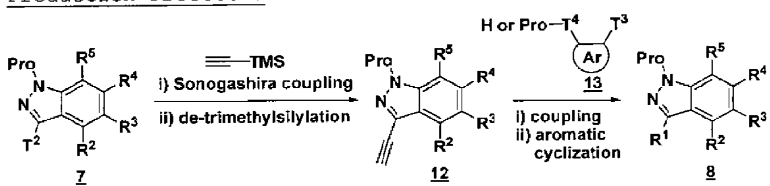
59



The compound 8 can also be produced by subjecting to Stille coupling with tributyl(1-ethoxyvinyl)tin, treating the resulting compound with N-bromosuccinimide to yield the bromoacetyl 11, and converting the bromoacetyl 11 to an aromatic ring, as shown in Production Process 8. The tributyl(1-ethoxyvinyl)tin for use in Stille coupling is commercially available. The amount of the tributyl(1-ethoxyvinyl)tin is from 1 to 3 equivalents to the raw material. Catalysts for use herein are not specifically limited, of which tetrakis(triphenylphosphine)palladium(0) is preferred. The amount of the catalyst is about 5% by mole relative to the raw material. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and preferred examples thereof are tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, toluene, and xylenes. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. The bromination can be performed by exchanging the solvent with tetrahydrofuran or dioxane, and adding about 1 equivalent of N-bromosuccinimide. The compound 11 can be converted into an aromatic ring by allowing the compound to react with, for

example, 2-aminopyridine or thiourea in the presence of a base. Such bases include, but are not specifically limited to, sodium hydrogencarbonate, sodium carbonate, potassium carbonate, and sodium hydride. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, alcohol solvents methanol or ethanol, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally 0°C to the reflux temperature of the solvent.

Production Process 9



As shown in Production Process 9, the compound 8 can also be produced by subjecting the compound 7 to Sonogashira coupling with trimethylsilylacetylene, detrimethylsililating the resulting compound to yield the compound 12, subjecting the compound 12 to coupling with the halogenated aromatic cyclic compound 13 having a hydroxyl group, amino group or thiol group at the ortho-position, each of which may be protected by a protecting group, and aromatically cyclizing the resulting compound under the same conditions after deprotecting the protecting

61

group, if any. The trimethylsilylacetylene for use in Sonogashira coupling is commercially available. The amount of the trimethylsilylacetylene is from 1 to 3 equivalents to the raw material. Catalysts for use herein include, but are not specifically limited to, palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), and tetrakis(triphenylphosphine)palladium(0). The amount of the catalyst is about 10% by mole relative to the raw material. Where necessary, an additive such as copper(I) iodide or triphenylphosphine can be added in an amount 1 to 2 times that of the catalyst. Bases for use herein include, but are not specifically limited to, triethylamine, diisopropylamine, and piperidine. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, of which dimethylformamide, tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, toluene, and xylenes are preferred. A reaction temperature is generally from room temperature to the reflux temperature of the solvent.

The detrimethylsilanization can be easily performed by using a fluorine anion or an acid. Such fluorine anions for use herein include, for example, tetrabutylammonium fluoride, hydrogen fluoride, potassium fluoride, and cesium fluoride. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated hydrocarbons such as

dichloromethane or chloroform, alcohol solvents such as methanol or ethanol, water, diethyl ether, tetrahydrofuran, dioxane, and toluene. A reaction temperature is from -20°C to the reflux temperature of the solvent. Acids for use herein include, for example, hydrochloric acid, sulfuric acid, and trifluoroacetic acid. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, alcohol solvents such as methanol or ethanol, diethyl ether, and tetrahydrofuran. A reaction temperature is from -20°C to the reflux temperature of the solvent.

Among the compounds 13, those commercially available will be purchased, and those not commercially available can be produced, for example, by protecting a hetero atom of an aromatic cyclic compound having a hydroxyl group, amino group or thiol group, treating the protected compound with an alkyllithium or lithium amide to yield a metal aryl, and halogenating the metal aryl.

Protecting groups for T^4 include, for example, *tert*-butyloxycarbonyl group, pivaloyl group, and methoxymethyl group. These protecting groups can be introduced by allowing an aromatic cyclic compound having a hydroxyl group, amino group or thiol group to react with di-*tert*-butyl dicarbonate, pivaloyl chloride or chloromethoxymethyl in the presence of a base. Such bases for use herein

include, but are not specifically limited to, triethylamine, 4-*N,N*-dimethylaminopyridine, sodium hydride, potassium *tert*-butoxide, lithium diisopropylamide, potassium carbonate, and sodium hydroxide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, halogenated hydrocarbons such as dichloromethane or chloroform, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from 0°C to the reflux temperature of the solvent.

The alkyllithium for converting the aromatic cyclic compound having the protected T^4 into the metal aryl includes, for example, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, and phenyllithium. Where necessary, an additive such as *N,N,N',N'*-tetramethylethylenediamine or hexamethylphosphoramide can be added. The lithium amide includes, for example, lithium diisopropylamide, and lithium 2,2,6,6-tetramethylpiperidide. Preferred examples of the halogenating agent are iodine, *N*-iodosuccinimide, bromine, and *N*-bromosuccinimide. Solvents for use herein are not specifically limited, as long as they are inert in the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene and toluene. A

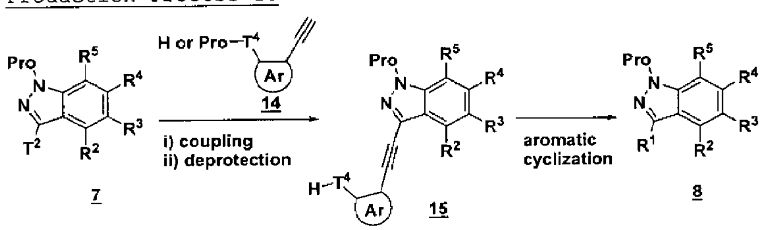
reaction temperature is from -78°C to room temperature.

The amount of the compound 13 for use in the coupling reaction between the compounds 12 and 13 is from 1 to 2 equivalents to the raw material 12. Catalysts for use herein include, but are not specifically limited to, palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), and tetrakis(triphenylphosphine)palladium(0). The amount of the catalyst is about 10% by mole relative to the raw material. Where necessary, an additive such as copper(I) iodide or triphenylphosphine can be added in an amount 1 to 2 times that of the catalyst. Bases for use herein include, but are not specifically limited to, triethylamine, diisopropylamine, and piperidine. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, of which dimethylformamide, tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, toluene, and xylenes are preferred. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. When the hetero atom of the compound 13 is not protected, the compound can undergo aromatic cyclization under these conditions.

When the hetero atom of the compound 13 is protected, the compound is deprotected after coupling and can undergo aromatic cyclization under the same conditions as in coupling. The protecting group of T^4 can be easily

deprotected by using an acid or a base. Such acids include, for example, hydrochloric acid, sulfuric acid, and trifluoroacetic acid. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated hydrocarbons dichloromethane or chloroform, alcohol solvents such as methanol or ethanol. A reaction temperature is from -20°C to the reflux temperature of the solvent. The base is not specifically limited and includes, for example, aqueous sodium hydroxide and aqueous potassium hydroxide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, alcohol solvents methanol or ethanol, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane. A reaction temperature is from room temperature to the reflux temperature of the solvent.

Production Process 10



The compound 8 can also be produced by subjecting the compound 7 to coupling with the compound 14, deprotecting the coupling product to yield the compound 15, and aromatically cyclizing the compound 15, as shown in

66

Production Process 10. The compound 14 can be synthetically prepared by subjecting the compound 13 to Sonogashira coupling with trimethylsilylacetylene, and detrimethylsilylating the coupling product. The trimethylsilylacetylene for use in Sonogashira coupling is commercially available. The amount of the trimethylsilylacetylene is from 1 to 3 equivalents to the raw material. Catalysts for use herein include, but are not specifically limited to, palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), and tetrakis(triphenylphosphine)palladium(0). The amount of the catalyst is about 10% by mole relative to the raw material. Where necessary, an additive such as copper(I) iodide or triphenylphosphine can be added in an amount 1 to 2 times that of the catalyst. Bases for use herein include, but are not specifically limited to, triethylamine, diisopropylamine, and piperidine. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, of which dimethylformamide, tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, toluene, and xylenes are preferred. A reaction temperature is generally from room temperature to the reflux temperature of the solvent.

The detrimethylsilanization can be easily performed by using a fluorine anion or an acid. Such fluorine anions for use herein include, for example, tetrabutylammonium

fluoride, hydrogen fluoride, potassium fluoride, and cesium fluoride. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated hydrocarbons dichloromethane or chloroform, alcohol solvents such as methanol or ethanol, water, diethyl ether, tetrahydrofuran, dioxane, and toluene. A reaction temperature is from -20°C to the reflux temperature of the solvent. Acids for use herein include, for example, hydrochloric acid, sulfuric acid, and trifluoroacetic acid. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, alcohol solvents such as methanol or ethanol. A reaction temperature is from -20°C to the reflux temperature of the solvent.

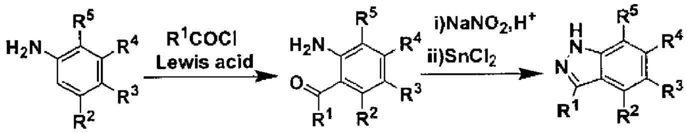
The amount of the compound 14 in the coupling reaction between the compounds 14 and 7 is from 1 to 2 equivalents to the raw material 7. Catalysts for use herein include, but are not specifically limited to, palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), and tetrakis(triphenylphosphine)palladium(0). The amount of the catalyst is about 10% by mole relative to the raw material. Where necessary, an additive such as copper(I) iodide or triphenylphosphine can be added in an amount 1 to 2 times that of the catalyst. Bases for use herein include,

but are not specifically limited to, triethylamine, diisopropylamine, and piperidine. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, of which dimethylformamide, tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, toluene, and xylenes are preferred. A reaction temperature is generally from room temperature to the reflux temperature of the solvent.

The protecting group of T^4 can be easily deprotected by using an acid or a base. Such acids include, for example, hydrochloric acid, sulfuric acid, and trifluoroacetic acid. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, alcohol solvents such as methanol or ethanol. A reaction temperature is from -20°C to the reflux temperature of the solvent. The base is not specifically limited and includes, for example, aqueous sodium hydroxide and aqueous potassium hydroxide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, alcohol solvents such as methanol or ethanol, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane. A reaction temperature is from room temperature to the reflux temperature of the solvent. By performing aromatic

cyclization of the compound 15 under the same conditions as in the coupling between the compound 7 and the compound 14, the compound 8 can be produced.

Production Process 11



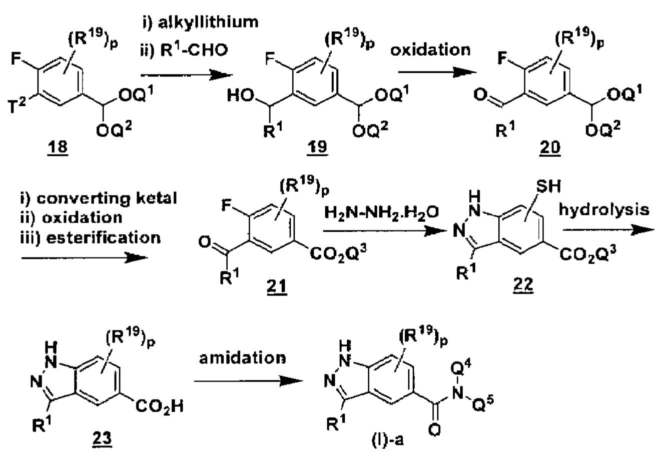
The compound (I) can also be produced by subjecting the aniline 16 and an aryl acid chloride to a Friedel-Crafts reaction to yield the ketone 17, converting the aniline derivative into a diazonium salt, reducing the diazonium salt with tin chloride, and closing the ring of the resulting compound. Lewis acids for use in the Friedel-Crafts reaction for the production of the ketone 17 include, for example, aluminium(III) chloride and ethylaluminium dichloride. Solvents for use herein are preferably halogen-containing solvents such as methylene chloride or chloroform. A reaction temperature is generally from -50°C to the reflux temperature of the solvent. The ketone 17 can be converted into the diazonium salt by allowing the ketone 17 to react with sodium nitrite in the presence of an acid. Reaction solvents for use herein include, for example, alcohol solvents such as methanol or ethanol, as well as hydrochloric acid, sulfuric acid, and acetic acid. A reaction temperature is generally

70

from 0°C to room temperature. The diazonium salt can be reduced and the indazole ring can be closed by allowing the diazonium salt to react with tin(II) chloride in the presence of an acid. Reaction solvents for use herein include, for example, alcohol solvents such as methanol or ethanol, as well as hydrochloric acid, sulfuric acid, and acetic acid. A reaction temperature is generally from 0°C to room temperature.

Practical production processes of 3-arylindazole compounds including production processes for the side chain moiety thereof will be illustrated below, but they are not limited thereto.

Production Process 12



The compound (I)-a can be produced by converting the ortho-halogenofluorobenzene 18 into a lithium aryl,

allowing the lithium aryl to react with an aryl aldehyde to yield the alcohol 19, oxidizing the alcohol 19 into the ketone 20, converting the acetal into the ester 21, treating the ester 21 with hydrazine into the indazole 22, hydrolyzing the indazole 22 into the carboxylic acid 23, and amidating the carboxylic acid 23.

Alkyllithiums for converting the ortho-halogenofluorobenzene 18 into the lithium aryl include, for example, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, and phenyllithium. Where necessary, an additive such as *N,N,N',N'*-tetramethylethylenediamine or hexamethylphosphoramide can be added. solvents for use herein are not specifically limited, as long as they are inert to the reaction, and preferred examples thereof are ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene and toluene. A reaction temperature is from -78°C to room temperature.

Oxidizing agents for oxidizing the alcohol 19 include, for example, manganese dioxide, sulfur trioxide-pyridine complex, N-methylmorhpoline-N-oxide, and chromic acid oxidizing agents. The oxidation can also be performed by Swern oxidation or Moffat oxidation. Solvents for use herein can be any solvents that are not involved in the reaction and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and

dimethylformamide. A reaction temperature is generally from -78°C to the reflux temperature of the solvent.

The ester 21 can be produced by treating with an acid into the aldehyde, oxidizing the aldehyde into the carboxylic acid, and esterifying the carboxylic acid. Acids for use in conversion into the aldehyde include, but are not specifically limited to, p-toluenesulfonic acid, pyridinium p-toluenesulfonate, hydrochloric acid, and sulfuric acid. Solvents for use herein can be any solvents that are not involved in the reaction and include, for example, alcohol solvents such as methanol or ethanol, as well as acetone, and tetrahydrofuran. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. Oxidizing agents for oxidizing the aldehyde into the carboxylic acid include, for example, Jones reagents and sodium chlorite. Solvents for use herein can be any solvents that are not involved in the reaction and include, for example, halogen-containing solvents such as methylene chloride or chloroform, as well as ethyl acetate, dimethylformamide, and dimethyl sulfoxide. A reaction temperature is generally from 0°C to the reflux temperature of the solvent. The carboxylic acid can be converted into the ester, for example, by allowing the carboxylic acid with an alkyl iodide in the presence of a base or to react with diazomethane. Examples of bases for use herein include sodium hydride, potassium carbonate, and

potassium *tert*-butoxide. A reaction temperature is generally from 0°C to the reflux temperature of the solvent.

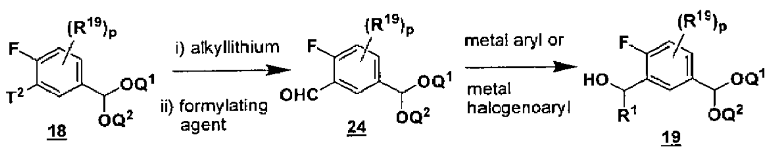
The cyclization of the ester 21 with hydrazine monohydrate can be performed in the absence of, or in the presence of, a solvent. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, alcohol solvents such as methanol, ethanol or propanol, as well as pyridine, dimethyl sulfoxide, benzene, and toluene. The amount of the hydrazine monohydrate is from 2 to 20 equivalents to the raw material. A reaction temperature is generally from 0°C to the reflux temperature of the solvent.

The ester 22 can be easily hydrolyzed by using, for example, aqueous sodium hydroxide or aqueous potassium hydroxide. Solvents for use herein can be any solvents that are not involved to the reaction and include, for example, alcohol solvents such as methanol or ethanol, as well as tetrahydrofuran, dioxane, and other ether solvents. A reaction temperature is generally from 0°C to the reflux temperature of the solvent.

The carboxylic acid 23 can be amidated by treating with an amine and a condensing agent. Such condensing agents include, for example, dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, and 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride. Where necessary, 1-hydroxybenzotriazole and/or N-hydroxysuccinimide can be added. Solvents for use herein can be any solvents that are not involved in the reaction and include, for example, halogen-containing solvents such as methylene chloride or chloroform, ether solvents such as ether or tetrahydrofuran, as well as ethyl acetate, dimethylformamide, and toluene. A reaction temperature is generally from room temperature to the reflux temperature of the solvent.

Production Process 13

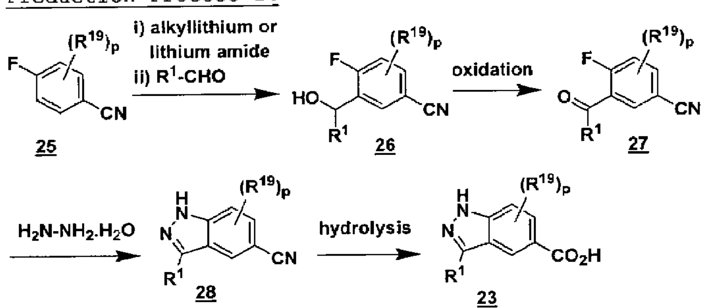


The alcohol 19 can also be produced by converting the ortho-halogenofluorobenzene 18 into a lithium aryl by the procedure of Production Process 12, allowing the lithium aryl to react with a formylation agent to yield the aldehyde 24, and allowing the aldehyde 24 to react with a metal aryl or metal halogenoaryl. Formylation agents for formylation of the lithium aryl prepared from the ortho-halogenofluorobenzene 18 by the procedure of Production Process 12 include, for example, dimethylformamide, *N*-formylpiperidine, and methylphenylformamide. Reaction solvents for use herein are not specifically limited, as

75

long as they are inert to the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene and toluene. A reaction temperature is from -78°C to room temperature. The metal aryl or metal halogenoaryl for the reaction with the aldehyde 24 can be easily prepared by the procedure of Production Process 2. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene and toluene. A reaction temperature is from -78°C to room temperature.

Production Process 14



The carboxylic acid 23 can also be produced by treating the fluorobenzene 25 with, for example, an alkyllithium or lithium amide to yield an lithium aryl, allowing the lithium aryl to react with an aryl aldehyde to yield the alcohol 26, oxidizing the alcohol 26 into the

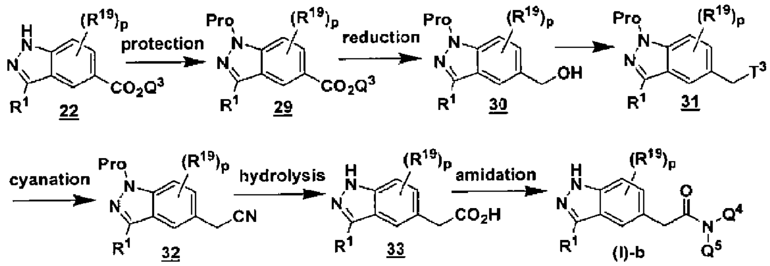
76

ketone 27, treating the ketone 27 with hydrazine to yield the indazole 28, and hydrolyzing the nitrile.

The alkyllithium for converting the fluorobenzene 25 into the lithium aryl includes, for example, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, and phenyllithium. Where necessary, an additive such as *N,N,N',N'*-tetramethylethylenediamine or hexamethylphosphoramide can be added. The lithium amide includes, for example, lithium diisopropylamide, and lithium 2,2,6,6-tetramethylpiperidide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and preferred examples thereof are ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene and toluene. A reaction temperature is from -78°C to room temperature. The compound 28 can be produced by oxidizing the alcohol and closing the indazole ring with the use of hydrazine monohydrate by the procedure of Production Process 12. The nitrile moiety of the compound 28 can be hydrolyzed by using an acid or a base. Such acids include, for example, hydrochloric acid and hydrous sulfuric acid. The reaction can be performed in the absence of, or in the presence of a solvent. Such solvents include, for example, alcohol solvents such as methanol, ethanol or propanol, as well as acetic acid. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. The base includes, for

example, sodium hydroxide and potassium hydroxide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, of which alcohol solvents such as methanol, ethanol or propanol are preferred. A reaction temperature is generally from room temperature to the reflux temperature of the solvent.

Production Process 15



The compound (I)-b can be prepared by protecting the 1-position of the ester 22 produced in Production Process 12 to yield the compound 29, reducing the compound 29 into the alcohol 30, converting the alcohol 30 into a sulfonate or halogen 31, converting the same into the cyano compound 32 and then into the carboxylic acid 33, and amidating the carboxylic acid 33. Protecting groups for protecting the 1-position of the ester 22 include, for example, *tert*-butyloxycarbonyl group, p-toluenesulfonyl group, triphenylmethyl group, and methoxymethyl group. The *tert*-butyloxycarbonyl group and *p*-toluenesulfonyl group can be introduced by allowing the ester 22 to react with di-tert-butyl dicarbonate or p-toluenesulfonyl chloride in the

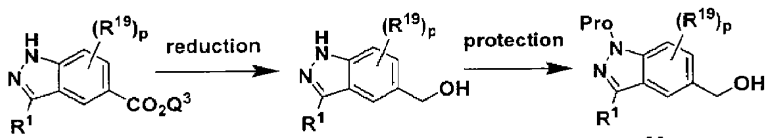
78

presence of a base. Such bases are not specifically limited, and preferred examples are triethylamine and 4-*N,N*-dimethylaminopyridine. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, halogenated hydrocarbons such as dichloromethane or chloroform, as well as pyridine, ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from 0°C to the reflux temperature of the solvent. The triphenylmethyl group and methoxymethyl group can be introduced by allowing the ester 22 to react with chlorotriphenylmethane or chloromethyl methyl ether in the presence of a base. Such bases are not specifically limited, and preferred examples are sodium hydride, potassium *tert*-butoxide, lithium diisopropylamide, potassium carbonate, and sodium hydroxide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as pyridine, ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from -20°C to the reflux temperature of the solvent. Reducing agents for reducing the ester moiety of the compound 29 include, for example, di-iso-butylaluminium hydride, lithium aluminium hydride,

and lithium borohydride. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene and toluene. A reaction temperature is generally from -20°C to the reflux temperature of the solvent. The alcohol 30 can be converted into the sulfonate by allowing the alcohol 30 to react with a sulfonyl chloride in the presence of a base. Examples of the sulfonyl chloride are methanesulfonyl chloride, and p-toluenesulfonyl chloride. Bases for use herein are not specifically limited and include, for example, triethylamine, 4-dimethylaminopyridine, and sodium hydride. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, halogen-containing solvents such as methylene chloride or chloroform, as well as pyridine, benzene, toluene, and dimethylformamide. A reaction temperature is from -20°C to the reflux temperature of the solvent. By performing the reaction in dichloromethane in the presence of triethylamine for a long time, a chloride can be obtained. The sulfonate and chloride can be converted into an iodide by allowing the same to react with about 1.1 equivalent of sodium iodide in acetone at room temperature. The nitrile

32 can be obtained by allowing the sulfonate or halide 31 to react with sodium cyanide or potassium cyanide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and include, for example, alcohol solvents such as methanol or ethanol, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as dimethylformamide, and dimethyl sulfoxide. A reaction temperature is from -20°C to the reflux temperature of the solvent. The nitrile 32 can be hydrolyzed by using an acid. Such acids include, for example, hydrochloric acid and hydrous sulfuric acid. The reaction can be performed in the absence of, or in the presence of a solvent. Such solvents include, for example, alcohol solvents such as methanol, ethanol or propanol, as well as acetic acid. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. In this reaction, the protecting group is removed concurrently. By amidating the carboxylic acid 33 by the procedure of Production Process 12, the compound (I)-b can be produced.

Production Process 16



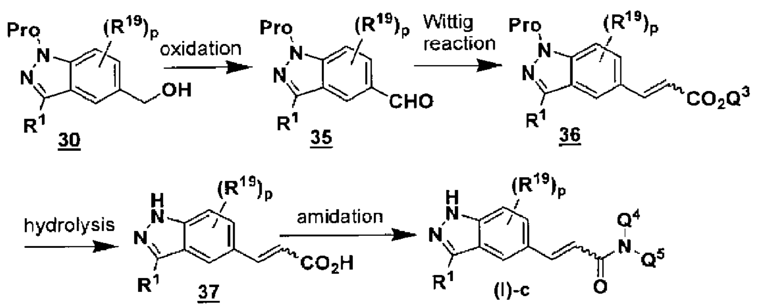
22 34 30

The compound 30 can also be produced by reducing the

81

ester 22 having a non-protected 1-position produced in Production Process 12, and protecting the 1-position. The ester 22 is reduced by the procedure of Production Process 15 to thereby yield the alcohol 34. Then, a protecting group is introduced into the 1-position of the alcohol 34 by the procedure of Production Process 15 to thereby yield the compound 30.

Production Process 17

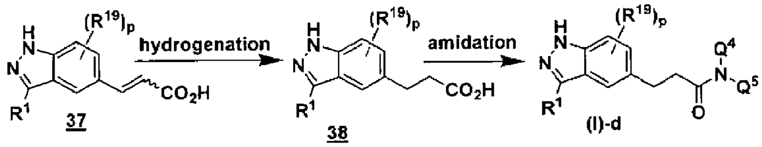


The compound (I)-c can be produced by oxidizing the alcohol 30 produced in Production Process 15 into the aldehyde 35, subjecting the aldehyde 35 to a Wittig reaction to yield the ester 36, converting the ester 36 into the carboxylic acid 37, and amidating the carboxylic acid 37. Oxidizing agents for oxidizing the alcohol 30 include, for example, manganese dioxide, sulfur trioxide-pyridine complex, N-methylmorpholine-N-oxide, and chromic acid oxidizing agents. The oxidation can also be performed by Swern oxidation or Moffat oxidation. Solvents for use herein can be any solvents that are not involved in the

reaction and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from -78°C to the reflux temperature of the solvent. Reagents for the Wittig reaction of the aldehyde 35 include, for example, triethyl phosphonoacetate, ethyl diphenylphosphonoacetate, and (carbethoxymethyl)triphenylphosphonium bromide. Bases for use herein include, but are not specifically limited to, sodium hydride, sodium hydrogencarbonate, potassium carbonate, sodium hydroxide, potassium *tert*-butoxide, and benzyltrimethylammonium hydroxide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, halogenated hydrocarbons such as dichloromethane or chloroform, as well as ethyl acetate, acetonitrile, toluene, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from 0°C to room temperature. By hydrolyzing the ester 36 according to the procedure of Production Process 12, the protecting group at the 1-position is concurrently deprotected, and the carboxylic acid 37 can thereby be produced. The compound (I)-c can be produced by amidating the carboxylic acid 37 according to the procedure of

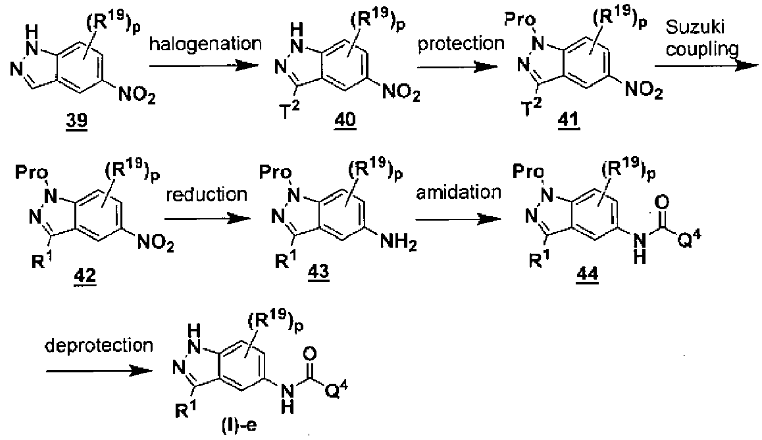
Production Process 12.

Production Process 18



The compound (I)-d can be produced by hydrogenating the carboxylic acid 37 produced in Production Process 17, and amidating the resulting compound. Hydrogenation reagents for the olefin moiety of the carboxylic acid 37 include, but are not specifically limited to, palladium-carbon, platinum oxide, and palladium hydroxide-carbon. The pressure of hydrogen is from 1 to 5 atom. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, halogenated hydrocarbons such as dichloromethane, chloroform, as well as ethyl acetate, acetonitrile, toluene, and dimethylformamide. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. The compound (I)-d can be produced by amidating the carboxylic acid 38 according to the procedure of Production Process 12.

Production Process 19



The compound (I)-e can be produced by halogenating the 3-position of the compound 39 into the compound 40, protecting the 1-position of the compound 40 to yield the compound 41, subjecting the compound 41 to Suzuki coupling with an arylboronic acid to yield the compound 42, reducing the compound 42 into the aniline 43, amidating the aniline 43 into the compound 44, and deprotecting the 1-position. Halogenation reagents for the 3-position of the compound 39 include, for example, *N*-bromosuccinimide, *N*-iodosuccinimide, *N*-chlorosuccinimide, and bromine. Where necessary, a radical reaction initiator such as 2,2'-azobisisobutyronitrile and benzoyl peroxide can be added. The amount of the halogenation reagent is from 1.05 to 1.2 equivalents to the raw material. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated

85

hydrocarbons such as dichloromethane, chloroform or carbon tetrachloride, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. Protecting groups for the 1-position of the compound 40 include, for example, *tert*-butyloxycarbonyl group, *p*-toluenesulfonyl group, and triphenylmethyl group. The *tert*-butyloxycarbonyl group and *p*-toluenesulfonyl group can be introduced by allowing the compound 40 to react with di-tert-butyl dicarbonate or p-toluenesulfonyl chloride in the presence of a base. Such bases are not specifically limited, and preferred examples thereof are triethylamine and 4-*N,N*-dimethylaminopyridine. Solvents for use herein are not specifically limited, as long as they are inert in the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, halogenated hydrocarbons such as dichloromethane or chloroform, as well as pyridine, ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from 0°C to the reflux temperature of the solvent. The triphenylmethyl group can be introduced by allowing the compound 40 to react with chlorotriphenylmethane in the presence of a base. Such bases include, but are not specifically limited to, sodium hydride, potassium *tert*-butoxide, lithium diisopropylamide,

potassium carbonate, and sodium hydroxide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is from -20°C to the reflux temperature of the solvent. Among arylboronic acids for use in Suzuki coupling of the compound **41**, those commercially available will be purchased, and those not commercially available can be easily prepared according to the procedure of Production Process 3. The amount of the arylboronic acid is from 1 to 3 equivalents to the raw material. Catalysts for use herein include, for example, palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), and tetrakis(triphenylphosphine)palladium(0). The amount of the catalyst is about 5% by mole relative to the raw material. Where necessary, a phosphine ligand in an amount of two times by mole that of the catalyst can be added. Such phosphine ligands include, for example, tri-*tert*-butylphosphine, 2-(di-*tert*-butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, and triphenylphosphine. Examples of bases for use herein are sodium hydrogencarbonate, sodium carbonate, potassium carbonate, cesium carbonate, and potassium fluoride. Solvents for use herein are not specifically limited, as long as they do not

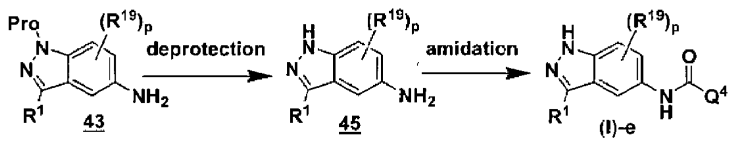
adversely affect the reaction, and include, for example, dimethylformamide, *N*-methylpyrrolidone, tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, and toluene. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. The nitro group of the compound 42 is reduced, for example, by hydrogenation by catalysis of palladium-carbon, palladium hydroxide-carbon, platinum oxide, or Raney's nickel, as well as reduction with tin(II) chloride, and reduction with iron-ammonium chloride. Solvents for use in the hydrogenation are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, alcohol solvents such as methanol or ethanol, halogen-containing solvents such as methylene chloride or chloroform, ether solvents such as tetrahydrofuran or diethyl ether, as well as ethyl acetate, dimethylformamide, and toluene. The amount of the hydrogenation catalyst is from 5% to 20% by weight relative to the raw material. The pressure of hydrogen is generally from 1 to 5 atom. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. Solvents for use in the reduction with tin(II) chloride include, for example, alcohol solvents such as methanol or ethanol, halogenated hydrocarbon solvents such as methylene chloride or chloroform, as well as dimethylformamide, *N*-methylpyrrolidone, and toluene. A reaction temperature is

generally from room temperature to the reflux temperature of the solvent. Solvents for use in the reduction with iron-ammonium chloride are preferably alcohol solvents such as aqueous methanol or aqueous ethanol. The amount of iron is from 3 to 10 equivalents to the raw material. The amount of the ammonium chloride is from 10% to 20% by weight relative to the raw material. A reaction temperature is generally the reflux temperature of the solvent. The aniline 43 can be amidated by treating with a carboxylic acid and a condensing agent. Such condensing agents include, for example, dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. Where necessary, 1-hydroxybenzotriazole and/or N-hydroxysuccinimide can be added. Solvents for use herein can be any solvents that are not involved in the reaction and include, for example, halogen-containing solvents such as methylene chloride or chloroform, ether solvents such as ether or tetrahydrofuran, as well as ethyl acetate, dimethylformamide, and toluene. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. The aniline 43 can also be amidated by allowing the aniline 43 to react with an acid chloride in the presence of a base. Such bases include, but are not specifically limited to, triethylamine,

diisopropylethylamine, and pyridine. Solvents for use herein can be any solvents that are not involved in the reaction and include, for example, halogen-containing solvents such as methylene chloride or chloroform, ether solvents such as ether or tetrahydrofuran, as well as ethyl acetate, and toluene. A reaction temperature is generally from -78°C to the reflux temperature of the solvent. The *tert*-butyloxycarbonyl group and triphenylmethyl group as the protecting group of the amide 44 can be easily deprotected or removed by using an acid. Such acids include, for example, hydrochloric acid, sulfuric acid, and trifluoroacetic acid. Where necessary, a radical scavenger such as thiophenol and tri-*iso*-propylsilane can be added. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, alcohol solvents such as methanol or ethanol, as well as anisole. A reaction temperature is generally from -20°C to the reflux temperature of the solvent. The *tert*-butyloxycarbonyl group and p-toluenesulfonyl group as the protecting agent can be easily deprotected by using a base. Such bases include, but are not specifically limited to, aqueous sodium hydroxide and aqueous potassium hydroxide. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, alcohol solvents such as methanol or

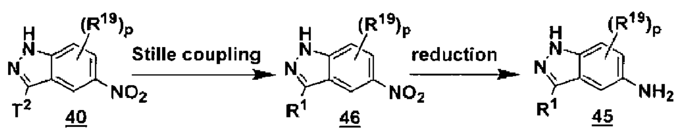
ethanol, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane. A reaction temperature is from room temperature to the reflux temperature of the solvent.

Production Process 20



The compound (I)-e can also be produced by deprotecting or removing, by the procedure of Production Process 19, the protecting group of the aniline 43 produced in Production Process 19 to yield the compound 45, and amidating the compound 45 according to the amidation procedure using a condensing agent as in Production Process 19.

Production Process 21

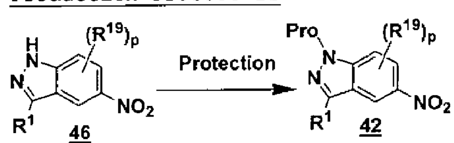


The aniline 45 can also be produced by subjecting the nitro derivative 40 having a non-protected 1-position produced in Production Process 19 to Stille coupling to yield the compound 46, and reducing the nitro group. Among aryltrialkyltins for use in the Stille coupling of the nitro derivative 40, those commercially available will be purchased, and those not commercially available can be

91

easily prepared according to the procedure of Production Process 5. The amount of the aryltrialkyltin is from 1 to 3 equivalents to the raw material. Catalysts for use herein include, for example, palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), and tetrakis(triphenylphosphine)palladium(0). The amount of the catalyst is about 5% by mole relative to the raw material. Where necessary, a phosphine ligand in an amount of two times by mole that of the catalyst can be added. Such phosphine ligands include, for example, tri-*tert*-butylphosphine, 2-(di-*tert*-butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, and triphenylphosphine. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, dimethylformamide, *N*-methylpyrrolidone, tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, toluene, and xylenes. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. By reducing the nitro derivative 46 according to the procedure of Production Process 19, the aniline 45 can be produced.

Production Process 22

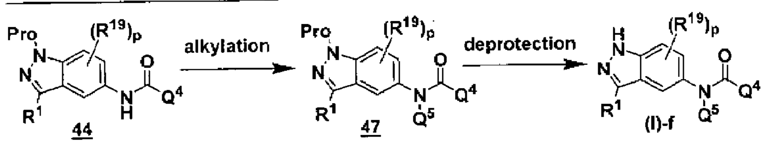


The compound 42 can also be produced by introducing,

92

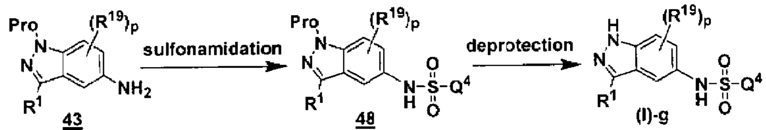
according to the procedure of Production Process 19, a protecting group into the compound 46 produced in Production Process 21.

Production Process 23



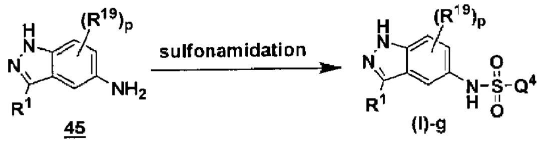
The compound (I)-f can be produced by alkylating the amide 44 produced in Production Process 19 to yield the *N*-alkylamide 47, and deprotecting the *N*-alkylamide 47. The amide 44 can be alkylated by allowing the amide 44 to react with a halogenoalkyl in the presence of a base. Such bases include, but are not specifically limited to, sodium hydride, potassium carbonate, potassium *tert*-butoxide, and potassium hydroxide. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, ether solvents such as ether, tetrahydrofuran or dioxane, as well as dimethylformamide, dimethyl sulfoxide, and toluene. A reaction temperature is generally from 0°C to the reflux temperature of the solvent. By deprotecting the N-alkylamide 47 according to the procedure of Production Process 19, the compound (I)-f can be produced.

Production Process 24



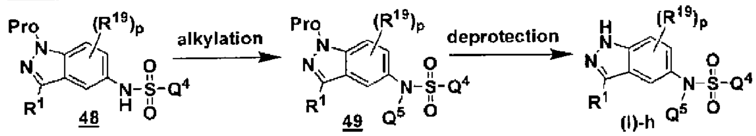
The compound (I)-g can be produced by converting the aniline 43 produced in Production Process 19 into the sulfonamide 48, and deprotecting the sulfonamide 48. The aniline 43 can be converted into the sulfonamide by allowing the aniline 43 to react with a sulfonyl chloride in the presence of a base. Such bases include, but are not specifically limited to, triethylamine, 4-dimethylaminopyridine, potassium carbonate, sodium hydride, and pyridine. The amount of the sulfonyl chloride is from 1.1 to 1.5 equivalents to the raw material. Reaction solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, ether solvents such as ether, tetrahydrofuran or dioxane, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, toluene, and dimethylformamide. Among them, ether, tetrahydrofuran, dioxane, and other ether solvents are preferred. A reaction temperature is generally from 0°C to room temperature. By deprotecting the sulfonamide 48 according to the procedure of Production Process 19, the compound (I)-g can be produced.

Production Process 25



The compound (I)-g can also be produced by converting the aniline 45 having a non-protected 1-position produced in Production Process 21 into a sulfonamide according to the procedure of Production Process 24.

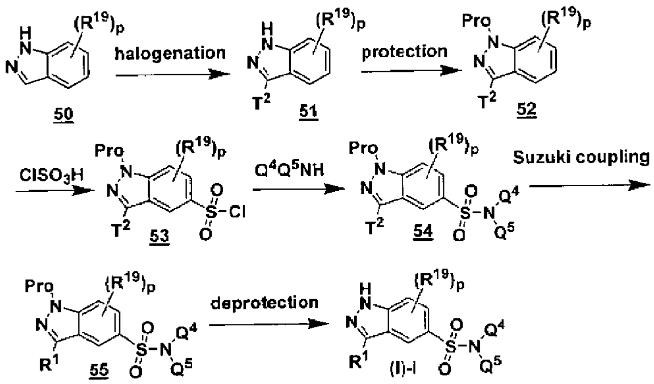
Production Process 26



The compound (I)-h can be produced by alkylating the sulfonamide 48 produced in Production Process 24, and deprotecting the resulting compound. The sulfonamide 48 can be alkylated by allowing the sulfonamide 48 to react with a halogenoalkyl in the presence of a base. Such bases include, but are not specifically limited to, sodium hydride, potassium carbonate, potassium tert-butoxide, and triethylamine. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, ether solvents such as ether, tetrahydrofuran or dioxane, as well as dimethylformamide, dimethyl sulfoxide, and toluene. A reaction temperature is generally from 0°C to the reflux temperature of the solvent. By deprotecting the sulfonamide 49 according to the procedure of Production

Process 19, the compound (I)-h can be produced.

Production Process 27

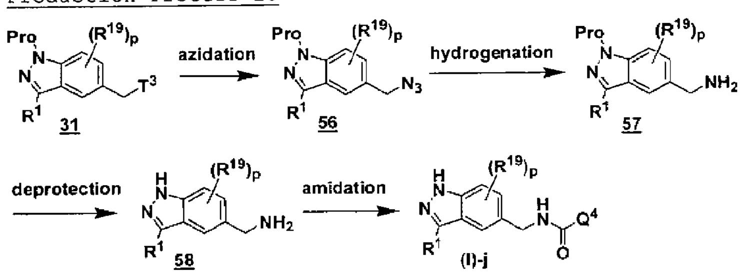


The compound (I)-i can be produced by subjecting the indazole 50 to halogenation and introduction of a protecting group according to the procedure of Production Process 19 to yield the compound 52, allowing the compound 52 to react with chlorosulfuric acid to yield sulfonyl chloride 53, converting the sulfonyl chloride 53 into the sulfonamide 54, subjecting the sulfonamide 54 to Suzuki coupling to yield the compound 55, and deprotecting the compound 55. The sulfonyl chloride 53 can be obtained by allowing the halogenated compound 52 to react with 1 to 2 equivalents of chlorosulfuric acid. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, halogen-containing solvents such as methylene chloride or chloroform. A reaction temperature is generally from 0°C

96

to room temperature. The sulfonyl chloride 53 can be sulfonamidated by allowing the sulfonyl chloride 53 to react with an amine in the presence of a base. An excess amount of the amine can serve as the base. Alternatively, for example, triethylamine, 4-dimethylaminopyridine, potassium carbonate, and sodium hydride can be added as the base. Reaction solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, ether solvents such as ether, tetrahydrofuran or dioxane, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, toluene, and dimethylformamide. A reaction temperature is generally from 0°C to room temperature. The sulfonamide 54 is subjected to Suzuki coupling with an arylboronic acid according to the procedure of Production Process 19 to thereby yield the compound 55. The compound 55 is then deprotected according to the procedure of Production Process 19 to thereby yield the compound (I)-i.

Production Process 28

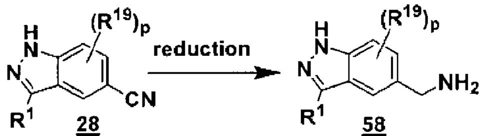


97

The compound (I)-j can be produced by converting the halide or sulfonate produced in Production Process 15 into an azide, reducing the azide into the amine 57, deprotecting the amine 57 to yield the compound 58, and amidating the compound 58. The azide 56 can be obtained by allowing the compound 31 to react with sodium azide or potassium azide. Reaction solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, alcohol solvents such as methanol or ethanol, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from -20°C to the reflux temperature of the solvent. The azide 56 can be reduced, for example, by hydrogenation by catalysis of palladium-calcium carbonate, palladium-carbon, palladium hydroxide-carbon, platinum oxide, and Raney nickel. Solvents for use in the hydrogenation are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, alcohol solvents such as methanol or ethanol, halogen-containing solvents such as methylene chloride or chloroform, ether solvents such as tetrahydrofuran or diethyl ether, as well as ethyl acetate, dimethylformamide, and toluene. The amount of the hydrogenation catalyst is from 5% to 20% by weight relative to the raw material. The pressure of

hydrogen is generally normal pressure (atmospheric pressure) but can be increased up to 5 atm. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. The 1-position of the amine 57 is deprotected according to the procedure of Production Process 3 to thereby yield the compound 58. Then, the compound 58 is amidated according to the procedure of Production Process 19 using a condensing agent to thereby yield the compound (I)-j.

<u>Production Process 29</u>

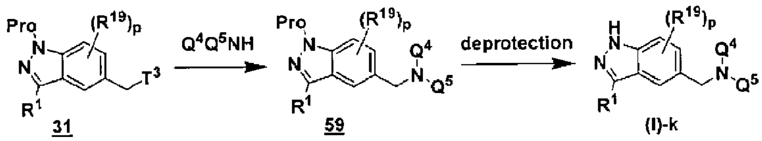


The compound 58 obtained in Production Process 28 can also be produced by reducing the nitrile 28 produced in Production Process 14. Reducing agents for use herein include, for example, sodium borohydride, lithium aluminium hydride, and aluminium hydride. Where necessary, an additive such as aluminium trichloride, boron trifluoride, cobalt chloride, and Raney nickel can be added. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, alcohol solvents such as methanol or ethanol, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane. A reaction temperature is from

99

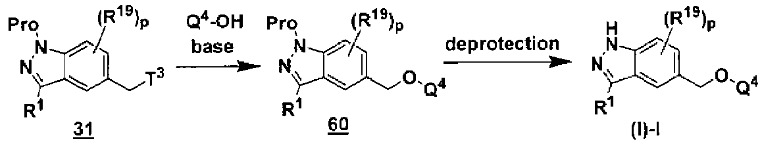
-78°C to the reflux temperature of the solvent.

Production Process 30



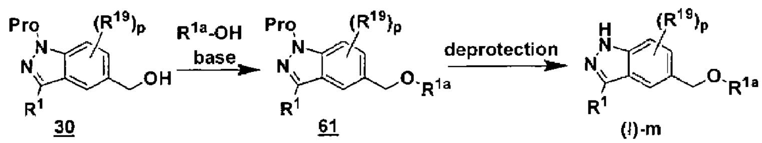
The compound (I)-k can be produced by converting the sulfonate or halide 31 obtained in Production Process 15 into the amine 59, and deprotecting the amine 59. The sulfonate or halide 31 can be aminated to react with an amine in the presence of a base. An excess amount of the amine can serve as the base. Alternatively, a base such as sodium hydride, potassium carbonate, and potassium *tert*-butoxide can be added. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, alcohol solvents such as methanol or ethanol, halogen-containing solvents such as methylene chloride or chloroform, ether solvents such as tetrahydrofuran or diethyl ether, as well as ethyl acetate, dimethylformamide, dimethyl sulfoxide, and toluene. A reaction temperature is generally from 0°C to the reflux temperature of the solvent. By deprotecting the amine 59 according to the procedure of Production Process 3, the compound (I)-k can be produced.

Production Process 31



The compound (I)-1 can be produced by allowing the sulfonate or halide 31 obtained in Production Process 15 to react with an alcohol in the presence of a base to thereby yield the ether 60, and deprotecting the ether 60. Bases for use in the etherification of the sulfonate or halide 31 include, but are not specifically limited to, sodium hydride, potassium carbonate, potassium *tert*-butoxide, and silver(I) oxide. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, halogen-containing solvents such as methylene chloride or chloroform, ether solvents such as tetrahydrofuran or diethyl ether, as well as ethyl acetate, dimethylformamide, dimethyl sulfoxide, and toluene. A reaction temperature is generally from 0°C to the reflux temperature of the solvent. By deprotecting the ether 60 according to the procedure of Production Process 3, the compound (I)-1 can be produced.

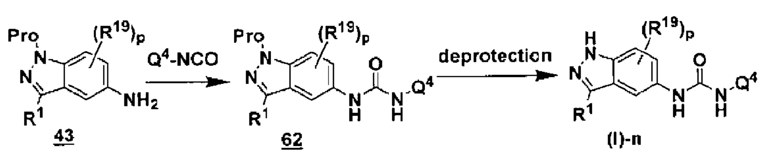
Production Process 32



101

The compound (I)-m can be produced by subjecting the alcohol 30 obtained in Production Process 15 and an aryl alcohol to Mitsunobu reaction to thereby yield the aryl ether 61, and deprotecting the aryl ether 61. The compound 61 can be produced, for example, by allowing the alcohol 30 to react with the aryl alcohol in the presence of triphenylphosphine and diethyl azodicarboxylate or diisopropyl azodicarboxylate. Solvents for use herein are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, halogen-containing hydrocarbons such as methylene chloride or chloroform, ether solvents such as tetrahydrofuran, diethyl ether or dioxane, as well as ethyl acetate, dimethylformamide, and toluene. A reaction temperature is generally from 0°C to room temperature. By deprotecting the compound 61 according to the procedure of Production Process 3, the compound (I)-m can be produced.

<u>Production Process 33</u>

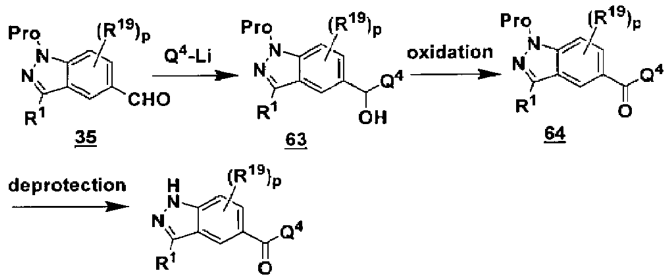


The compound (I)-n can be produced by allowing the aniline 43 obtained in Production Process 19 to react with an isocyanate to yield the urea 62, and deprotecting the urea 62. Solvents for use in the conversion of the aniline

102

43 into the urea are not specifically limited, as long as they do not adversely affect the reaction, and include, for example, halogen-containing solvents such as methylene chloride or chloroform, ether solvents such as tetrahydrofuran or diethyl ether, as well as ethyl acetate, dimethylformamide, dimethyl sulfoxide, and toluene. A reaction temperature is generally from 0°C to the reflux temperature of the solvent. By deprotecting the urea 62 according to the procedure of Production Process 19, the compound (I)-n can be produced.

Production Process 34

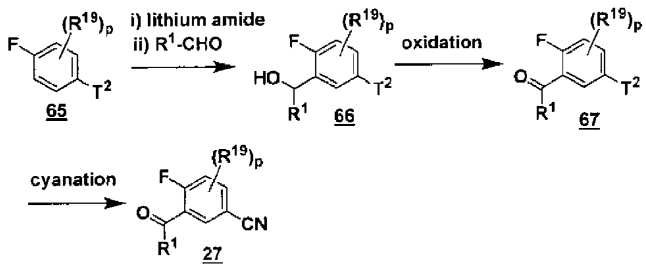


The compound (I)-o can be produced by allowing the aldehyde 35 obtained in Production Process 17 to react with an alkyllithium, a Grignard reagent, a metal aryl, or a metal halogenoaryl to yield the alcohol 63, oxidizing the alcohol 63 into the ketone 64, and deprotecting the ketone 64. The alkyllithium for the reaction of the aldehyde 35 is commercially available. The Grignard reagent can be prepared by using an alkyl halide and magnesium. Among

103

metal aryls or metal halogenoaryls for use herein, those commercially available will be purchased, and those not commercially available can be easily prepared according to the procedure of Production Process 3. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene, and toluene. A reaction temperature is from -78°C to room temperature. Oxidizing agents for oxidizing the alcohol 63 include, for example, manganese dioxide, sulfur trioxide-pyridine complex, N-methylmorpholine-N-oxide, and chromic acid oxidizing agents. The oxidation can also be performed by Swern oxidation or Moffat oxidation. Solvents for use herein can be any solvents that are not involved in the reaction and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, as well as ethyl acetate, acetonitrile, dimethyl sulfoxide, and dimethylformamide. A reaction temperature is generally from -78°C to the reflux temperature of the solvent. By deprotecting the ketone 64 according to the procedure of Production Process 3, the compound (I)-o can be produced.

Production Process 35

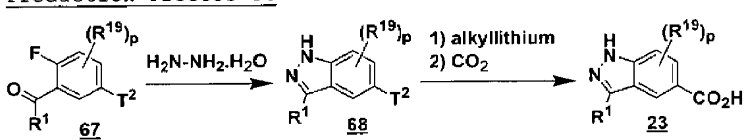


The compound 27 obtained in Production Process 14 can also be produced by treating the fluorobenzene 65 with, for example, lithium amide to yield a lithium aryl, allowing the lithium aryl to react with an aryl aldehyde to yield the alcohol 66, oxidizing the alcohol 66 into a ketone, and replacing T^2 a with cyano group.

Lithium amides for converting the fluorobenzene 65 into the lithium aryl include, for example, lithium diisopropylamide, and lithium 2,2,6,6-tetramethylpiperidide. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, and preferred examples thereof are ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene, and toluene. A reaction temperature is from -78°C to room temperature. By oxidizing the alcohol 66 according to the procedure of Production Process 12, the compound 67 can be produced. Reagents for converting the compound 67 into the nitrile 27 include zinc cyanide, lithium cyanide, sodium cyanide, or potassium cyanide in combination with a transition metal catalyst such as

tetrakis(triphenylphosphine)palladium, tris(dibenzylideneacetone)dipalladium, dichlorobis(triphenylphosphine)palladium, and palladium diacetate. The reaction may be performed in the presence of a catalytic amount of copper iodide or a phosphine ligand such as triphenylphosphine and 1,1'-bis(diphenylphosphino)ferrocene. Preferred examples of solvents for use herein are dimethylformamide, N-methylpyrrolidone, propionitrile, and acetonitrile. A reaction temperature is preferably within a range from 80°C to 150°C. The nitrile 27 can also be produced by allowing the compound 67 to react with copper cyanide in a solvent such as dimethylformamide or N-pyrrolidone at a temperature within a range from 140°C to 200°C.

Production Process 36



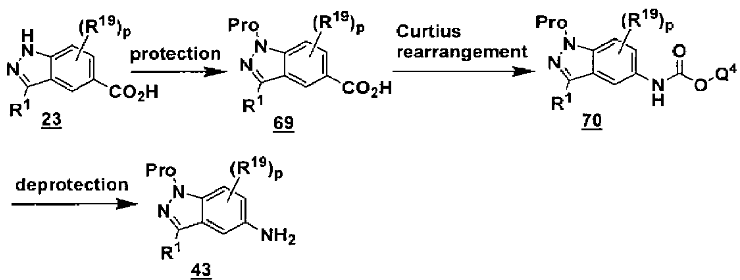
The carboxylic acid 23 obtained in Production Process 12 can also be produced by treating the compound 67 obtained in Production Process 35 with hydrazine to yield the indazole 68, converting the indazole 68 into a lithium aryl with the use of an alkyl lithium, and allowing the lithium aryl to react with carbon dioxide.

By closing the indazole ring of the compound 67 with the use of hydrazine monohydrate according to the procedure

of Production Process 12, the indazole 68 can be produced. The alkyllithium for converting the indazole 68 into the lithium aryl includes, for example, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, and phenyllithium. Where necessary, an additive such as *N,N,N',N'*-tetramethylethylenediamine or hexamethylphosphoramide can be added.

By allowing the lithium aryl to react with carbon dioxide gas or dry ice, the carboxylic acid 23 can be produced. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction, and preferred examples thereof are ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, as well as benzene, and toluene. A reaction temperature is from -78°C to room temperature.

Production Process 37



The aniline 43 obtained in Production Process 19 can also be produced by protecting the 1-position of the carboxylic acid 23 obtained in Production Process 12 to

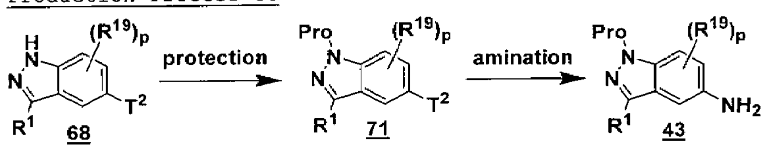
107

yield the compound 69, subjecting the compound 69 to Curtius rearrangement to yield the carbamate 70, and deprotecting the carbamate.

By introducing a protecting group into the 1-position according to the procedure of Production Process 15, the compound 69 can be produced. The compound 69 can be subjected to Curtius rearrangement by treating the compound 69 with, for example, diphenylphosphoryl azide and an amine such as triethylamine or diisopropylethylamine to yield an isocyanate, and allowing the isocyanate to react with an alcohol, or by treating the compound 69 with, for example, thionyl chloride or oxalyl chloride to yield an acid chloride, treating the acid chloride with lithium azide, sodium azide or potassium azide to yield an isocyanate, and allowing the isocyanate to react with an alcohol. The alcohol for use herein is not specifically limited, of which benzyl alcohol and *tert*-butanol are especially preferred. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, toluene, benzene, tetrahydrofuran, and dioxane. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. A *tert*-butyloxycarbonyl group as the protecting group of the carbamate 70 can be easily deprotected or removed by using an acid. Such acids include, for example, hydrochloric acid, sulfuric acid, and trifluoroacetic acid. Where

necessary, a radical scavenger such as thiophenol or tri-*iso*-propylsilane can be added. Solvents for use herein are not specifically limited, as long as they are inert in the reaction, and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform, as well as anisole. A benzyloxycarbonyl group as the protecting group can be easily deprotected or removed by hydrogenation. Reagents for use in the hydrogenation include, but are not specifically limited to, palladium-carbon, platinum oxide, and palladium hydroxide-carbon. The pressure of hydrogen is from 1 to 5 atm. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, ether solvents such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, halogenated hydrocarbons such as dichloromethane or chloroform, as well as ethyl acetate, acetonitrile, toluene, and dimethylformamide. A reaction temperature is generally from room temperature to the reflux temperature of the solvent.

Production Process 38



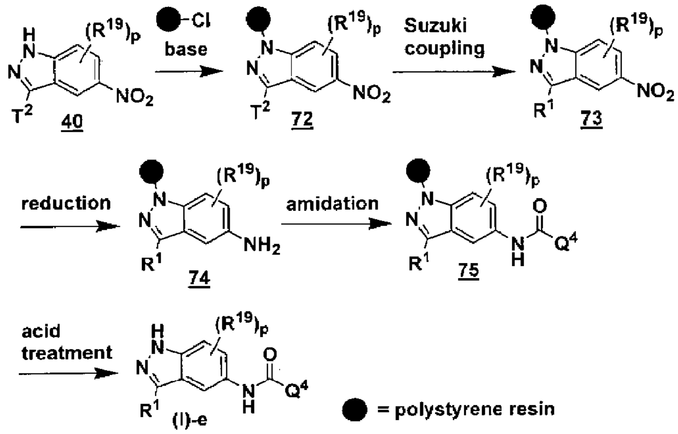
The aniline 43 obtained in Production Process 19 can also be produced by protecting the 1-position of the compound 68 obtained in Production Process 36 to yield the

109

compound 71, and then aminating T^2.

By introducing a protecting group into the 1-position of the compound 68 according to the procedure of Production Process 15, the compound 71 can be produced. Palladium catalysts for use in amination of the compound 71 include, for example, tris(dibenzylideneacetone)dipalladium, and palladium diacetate. Phosphine ligands for use herein include, for example, 2,2'-bis(diphenylphosphino)-1,1'-naphthyl, 1,1'-bis(diphenylphosphino)ferrocene, and tri(*tert*-butyl)phosphine. Bases for use herein include, for example, sodium *tert*-butoxide, potassium *tert*-butoxide, and cesium carbonate. An ammonia equivalent for use herein is not specifically limited and is preferably benzophenoneimine. Acids for use in hydrolysis of the resulting imine derivative include, but are not specifically limited to, diluted hydrochloric acid and diluted sulfuric acid. Solvents for use in the reaction are not specifically limited, as long as they are inert to the reaction, and include, for example, toluene, tetrahydrofuran, dioxane, and dimethoxyethane. A reaction temperature is generally from room temperature to 120°C.

Production Process 39



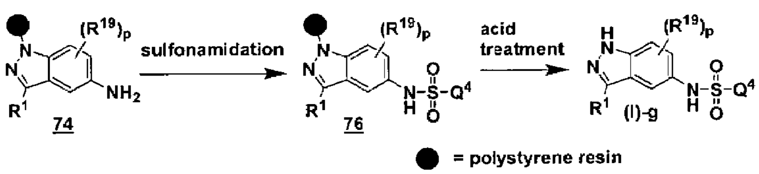
The compound (I)-e can also be produced by combining, with a resin, the 1-position of the compound 40 obtained in Production Process 19 to yield the compound 72, subjecting the product to Suzuki coupling with an arylboronic acid to yield the compound 73, reducing the product into the aniline 74, amidating the product into the compound 75, and then exciding the target compound from the resin using an acid. Advantages of the synthesis using a resin are that a multitude of a target compound can be synthetically prepared at once, that a purification procedure in each step is not required, as an excess reagent can be removed by washing, and that the resin itself serves as a protecting group. By allowing the compound 40 to react with the resin in the presence of a base, 72 can be obtained. Such bases include, but are not specifically limited to, triethylamine, diisopropylethylamine, 4-*N*,*N*-

dimethylaminopyridine, sodium hydride, potassium *tert*-butoxide, and potassium carbonate. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and can hold affinity for the resin, and include, for example, ether solvents tetrahydrofuran or dioxane, as well as dimethyl sulfoxide, dimethylformamide, N-methylpyrrolidone, ethyl acetate, and acetonitrile. A reaction temperature is generally from 0°C to the reflux temperature of the solvent. Among arylboronic acids for use in Suzuki coupling of the compound 72, those commercially available will be purchased, and those not commercially available can be easily prepared according to the procedure of Production Process 3. The arylboronic acid is used in excess. Catalysts for use herein include, for example, palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), and tetrakis(triphenylphosphine)palladium(0). The amount of the catalyst is about 5% by mole relative to the arylboronic acid. Where necessary, a phosphine ligand in an amount of two times by mole that of the catalyst can be added. Such phosphine ligands include, for example, tri-*tert*-butylphosphine, 2-(di-*tert*-butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, and triphenylphosphine. Bases for use herein include, for example, sodium hydrogencarbonate, sodium carbonate, potassium carbonate, cesium carbonate, and potassium fluoride. Solvents for use

herein are not specifically limited, as long as they are inert to the reaction and can hold affinity for the resin, and include, for example, dimethylformamide, *N*-methylpyrrolidone, tetrahydrofuran, dioxane, and diethylene glycol dimethyl ether. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. The nitro group of the compound 73 can be reduced, for example, by reduction with tin(II) chloride or reduction with iron-ammonium chloride. Solvents for use in the reduction with tin(II) chloride include, for example, alcohol solvents such as methanol or ethanol, dimethylformamide, and *N*-methylpyrrolidone. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. Solvents for use in the reduction with iron-ammonium chloride are preferably alcohol solvents such as aqueous methanol or aqueous ethanol. The amount of iron is from 3 to 10 equivalents to the raw material. The amount of the ammonium chloride is from 10% to 20% by weight relative to the raw material. A reaction temperature is generally the reflux temperature of the solvent. The aniline 74 can be amidated by treating with a carboxylic acid and a condensing agent. Such condensing agents include, for example, dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. Where

necessary, 1-hydroxybenzotriazole and/or N-hydroxysuccinimide can be added. Solvents for use herein are not specifically limited, as long as they are inert to the reaction and can hold affinity for the resin, and include, for example, ether solvents such as tetrahydrofuran or dioxane, as well as dimethylformamide, N-methylpyrrolidone, and ethyl acetate. A reaction temperature is generally from room temperature to the reflux temperature of the solvent. The compound (I)-e can be easily excided from the resin using an acid. Such acids include, for example, hydrochloric acid, sulfuric acid, and trifluoroacetic acid. Where necessary, a radical scavenger such as thiophenol or tri-*iso*-propylsilane can be added. Solvents for use herein are not specifically limited, as long as they are inert to the reaction, and include, for example, halogenated hydrocarbons such as dichloromethane or chloroform. A reaction temperature is from room temperature to the reflux temperature of the solvent.

Production Process 40



The compound (I)-g can also be produced by converting the aniline 74 obtained in Production Process 39 into the sulfonamide 76, and then exciding the target compound from

114

the resin using an acid. The aniline 74 can be converted into the sulfonamide by allowing it to react with a sulfonyl chloride in the presence of a base. Such bases include, but are not specifically limited to, triethylamine, 4-dimethylaminopyridine, potassium carbonate, and sodium hydride. The amount of the base is from 0.9 to 1.1 equivalents to the sulfonyl chloride. Reaction solvents for use herein are not specifically limited, as long as they are inert to the reaction and can hold affinity for the resin, and include, for example, ether solvents such as tetrahydrofuran or dioxane, as well as dimethyl sulfoxide, *N*-methylpyrrolidone, dimethylformamide, ethyl acetate, and acetonitrile. Among them, ether solvents such as tetrahydrofuran or dioxane are preferred. A reaction temperature is generally from 0°C to room temperature. By exciding from the resin according to the procedure of Production Process 39, the compound (I)-g can be produced.

Material compounds for use in the production of the compounds of the present invention can be in the form of salts and/or hydrates and are not specifically limited as long as they do not adversely affect the reactions. When the compounds (I) according to the present invention are obtained as free compounds, they can be converted into acceptable salts of the above-mentioned compound (I) according to a conventional procedure. Various isomers such as geometrical isomers, optical isomers due to an

asymmetric carbon, stereoisomers, and tautomers obtained as the compounds (I) according to the present invention can be purified and isolated according to a conventional separation means. Such separation means include, for example, recrystallization, diastereomeric salt method, enzymatic resolution, and a variety of chromatography such as thin layer chromatography, column chromatography or gas chromatography.

The term "salt(s)" as used in the present description is not specifically limited, as long as it can form a salt with the compound according to the present invention and is pharmacologically acceptable. Preferred examples of the salts are hydrohalides such as hydrofluorides, hydrochlorides, hydrobromides or hydroiodides; salts of inorganic acids, such as sulfates, nitrates, perchlorates, phosphates, carbonates or bicarbonates; salts of organic carboxylic acids, such as acetates, trifluoroacetates, oxalates, maleates, tartrates, fumarates or citrates; salts of organic sulfonic acids, such as methanesulfonates, trifluoromethanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates or camphorsulfonates; salts of amino acids, such as aspartates or glutamates; quaternary amine salts; alkali metal salts such as sodium salts or potassium salts; alkaline earth metal salts such as magnesium salts or calcium salts. More preferred examples of the "pharmacologically acceptable salt(s)" are

hydrochlorides, oxalates and trifluoroacetates.

The compounds represented by the formula (I) according to the present invention, a salt thereof or a hydrate of them can be formulated into pharmaceutical preparations according to a conventional procedure. Preferred dosage forms are tablets, powders, fine granules, granules, coated tablets, capsules, syrups, troches, inhalants, suppositories, injections, ointments, ophthalmic ointments, eye drops, nasal drops, ear drops, cataplasms, and lotions. In the formulation, generally used fillers, binders, disintegrators, lubricants, coloring agents, and flavoring agents, as well as stabilizers, emulsifiers, absorbefacients, surfactants, pH adjusting agents, antiseptics, and antioxidants according to necessity can be used. They can be formulated according to a conventional procedure using components generally used as raw materials for pharmaceutical preparations. Examples of such components include (1) animal or vegetable oils such as soybean oil, beef tallow or synthetic glycerides; (2) hydrocarbons such as liquid paraffins, squalane or solid paraffins; (3) ester oils such as octyldodecyl myristate or isopropyl myristate; (4) higher alcohols such as cetostearyl alcohol or behenyl alcohol; (5) silicon resins; (6) silicon oils; (7) surfactants such as polyoxyethylene fatty acid esters, sorbitan fatty acid esters, glycerin fatty acid esters, polyoxyethylene sorbitan fatty acid

esters, polyoxyethylene hydrogenated castor oils or polyoxyethylene-polyoxypropylene block copolymers; (8) water-soluble polymers such as hydroxyethyl cellulose, poly(acrylic acid)s, carboxyvinyl polymers, polyethylene glycol, polyvinylpyrrolidone or methylcellulose; (9) lower alcohols such as ethanol or isopropanol; (10) polyhydric alcohols such as glycerol, propylene glycol, dipropylene glycol or sorbitol; (11) sugars such as glucose or sucrose; (12) inorganic powders such as silicic anhydride, magnesium aluminium silicate or aluminium silicate; and (13) purified water.

1) The fillers include, for example, lactose, corn starch, sucrose, glucose, mannitol, sorbitol, crystalline cellulose, and silicon dioxide; 2) the binders include, for example, polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, gum arabic, gum tragacanth, gelatin, shellac, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, polypropylene glycol-polyoxyethylene block polymers, meglumine, calcium citrate, dextrin, and pectin; 3) the disintegrators include, for example, starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin, pectin, and carboxymethylcellulose calcium; 4) the lubricants include, for example, magnesium stearate, talc, polyethylene glycol, silica, and hardened vegetable oils; 5) the coloring agents

can be any coloring agents which are approved to add to pharmaceutical preparations; 6) the flavoring agents include, for example, cocoa powder, menthol, aromatic powder, peppermint oil, borneol, and cinnamon powder; 7) the antioxidants can be any antioxidants which are approved to add to pharmaceutical preparations such as ascorbic acid or α-tocopherol.

1) As oral preparations, the compound according to the present invention or the salt thereof is compounded with a filler, and if necessary, a binder, disintegrator, lubricant, coloring agent, flavoring agent, and other components, and the resulting mixture is formulated according to a conventional procedure into a powder, fine granules, granules, tablet, coated tablet, capsule, etc. 2) The tablets and granules can be appropriately coated with, for example, sugar or gelatin, or other according to necessity. 3) Liquid formulations such as syrups, injection preparations or eye droppers can be prepared in a conventional method, by adding a pH adjusting agents, solubilizer, and isotonizing agent, and if necessary, a solubilizing agent, stabilizer, buffer, suspending agent, antioxidant, and other components. The liquid formulations can also be formed into freeze-dried products. The injections can be administered intravenously, subcutaneously and/or intramuscularly. Preferred examples of the suspending agents are methylcellulose, polysorbate

80, hydroxyethyl cellulose, gum arabic, tragacanth powder, sodium carboxymethylcellulose, and polyoxyethylene sorbitan monolaurate; preferred examples of solubilizers are polyoxyethylene hardened caster oil, polysorbate 80, nicotinamide, and polyoxyethylene sorbitan monolaurate; preferred examples of the stabilizers are sodium sulfite, sodium metasulfite, and ether; preferred examples of the preservatives are methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol, and chlorocresol. 4) External preparations can be produced according to a conventional procedure not specifically limited. Base materials for use herein can be any raw materials generally used in, for example, pharmaceutical preparations, quasi drugs, and cosmetics. Such raw materials include, for example, animal or vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicon oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals, and purified water. If necessary, any of pH adjusting agents, antioxidants, chelating agents, antiseptics and antimolds, coloring agents, and flavors can be added. In addition, components having differentiation-inducing action, blood-flow accelerators, bactericides, anti-inflammatory agents, cell activators, vitamins, amino acids, humectants, keratolytic agents, and other components can be added according to necessity.

The dose of the pharmaceutical preparation according to the present invention varies depending on the degree of symptom, age, sex, body weight, administration mode, type of the salt, difference in sensibility to the drug, concrete type of the disease, and other factors. Generally, in oral administration, the pharmaceutical preparations may be administered at a daily dose of about 30 μg to about 1000 mg, preferably about 100 μg to about 500 mg, and more preferably about 100 μg to about 100 mg for an adult in one to several divided doses. In injection administration, they may be administered at a daily dose of about 1 to about 3000 μg/kg, and preferably about 3 to about 1000 μg/kg for an adult in one to several divided doses.

The present invention can provide novel indazole compounds. The compounds (I) according to the present invention or the salts thereof have excellent inhibitory action on c-Jun amino-terminal kinases, especially on JNK 3. Accordingly, the compounds (I) according to the present invention or the salts thereof, and pharmaceutical compositions containing the same are useful as therapeutic agents or prophylactic agents for an immunologic disease, inflammatory disease and/or neurodegenerative disease. They are particularly useful as therapeutic agents or prophylactic agents, for example, for acute neurodegenerative diseases such as acute stage of cerebrovascular disorder, head injury, spinal code injury,

neuropathy due to hypoxia, and neuropathy due to hypoglycemia; chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis or spinocerebellar degeneration; epilepsy; hepatic encephalopathy; peripheral neuropathy; Parkinsonian syndrome; spastic paralysis; pain; neuralgia; infectious encephalomyelitis; cerebrovascular dementia; or dementia or neurological symptom due to meningitidis.

Examples

The following production examples, examples, and test examples are indicated by illustration, and the compounds of the present invention are never restricted by the following examples. Those skilled in the art can modify not only the following examples but also the claims according to the present description in various ways to exert the most of the present invention, and such modifications and variations are also included within the scope of the appended claims relating to the present description.

PRODUCTION EXAMPLE I-1-a

4-Fluoro-3-[(3-fluorophenyl)(hydroxy)methyl]benzonitrile

In an atmosphere of nitrogen gas, 76.3 ml of 1.56 M solution of n-butyllithium in hexane was added to a solution of 11.1 g of *N,N*-diisopropylamine in 200 ml

tetrahydrofuran under ice-cooling, and the mixture was stirred at the same temperature for 15 minutes. After cooling to -78°C, a solution of 12.1 g of 4-fluorobenzonitrile in 40 ml tetrahydrofuran was added dropwise. After stirring at the same temperature for 45 minutes, 10.6 ml of 3-fluorobenzaldehyde was added dropwise. After stirring at the same temperature for 25 minutes, saturated aqueous ammonium chloride solution was added and the solvent was removed. To the residue was added 150 ml of ethyl acetate, and the mixture was sequentially washed with 1 N hydrochloric acid, water, saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 3:97 to 1:19), and the resulting crystals were recrystallized from diisopropyl ether-hexane, to give 12.7 g of the title compound as pale yellow needles.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 5.97 (1H, d, J = 4.4 Hz), 6.40 (1H, d, J = 4.4 Hz), 7.09 (1H, td, J = 8.4, 2.8 Hz), 7.17 (1H, d, J = 8.0 Hz), 7.21 (1H, d, J = 10.0 Hz), 7.33-7.44 (2H, m), 7.86 (1H, m), 8.04 (1H, dd, J = 2.0, 6.8 Hz).

PRODUCTION EXAMPLE I-1-b

3-(3-Fluorophenyl)-1*H*-5-indazolecarbonitrile

To a solution of 12.5 g of 4-fluoro-3-[(3-fluorophenyl)(hydroxy)methyl]benzonitrile in 200 ml

methylene chloride was added 43.8 g of activated manganese dioxide, and the resulting mixture was stirred at room temperature for 10 hours and at 35°C for further 9 hours. Then, the manganese dioxide was filtered off through Celite. After removing the solvent by distillation, the residue was dissolved in 25 ml of tetrahydrofuran and 25 ml of methanol. 12 ml of hydrazine monohydrate was added, followed by stirring at room temperature for 7 hours. The reaction mixture was added with 150 ml of water, and ice-cooled. Then, the resulting crystals were collected by filtration. The crystals were dried in vacuo, to give 11.6 g of the title compound as yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.30 (1H, td, J = 8.0, 2.8 Hz), 7.58 (1H, td, J = 8.0, 6.4 Hz), 7.75 (1H, dd, J = 8.8, 1.6 Hz), 7.79 (1H, d, J = 8.8 Hz), 7.83 (1H, dd, J = 10.4, 2.8 Hz), 7.93 (1H, d, J = 8.0 Hz), 8.78 (1H, s), 13.88 (1H, s).

PRODUCTION EXAMPLE I-1-c

3-(3-Fluorophenyl)-1*H*-5-indazolecarboxylic acid

To 10.0 g of 3-(3-fluorophenyl)-1*H*-5-indazolecarbonitrile were sequentially added 50 ml of glacial acetic acid, 15 ml of water and 12 ml of concentrated sulfuric acid, and the mixture was stirred at 110°C for 6.5 hours. After standing to cool, the reaction mixture was added with 150 ml of ice-water, and the resulting crystals were collected by filtration. The resulting crystals were dried in vacuc, to give 10.7 g of

124

the title compound as beige orange-pink crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.28 (1H, dt, J = 2.8, 10.1 Hz), 7.61 (1H, dt, J = 6.2, 8.2 Hz), 7.67 (1H, d, J = 8.8 Hz), 7.72 (1H, ddd, J = 1.5, 2.8, 10.1 Hz), 7.82 (1H, d, J = 8.2 Hz), 7.97 (1H, d, J = 8.8 Hz), 8.63 (1H, s), 12.80-12.95 (1H, bs), 13.67 (1H, s)

PRODUCTION EXAMPLE I-2-a

3-(3-Fluorophenyl)-1*H*-7-indazolecarbonitrile

A total of 637 mg of the title compound as yellow crystals was obtained from 2.42 g of 2-fluorobenzonitrile by the procedures of Production Examples I-1a and I-1b.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.30 (1H, td, J = 8.0, 2.4 Hz), 7.40 (1H, t, J = 8.0 Hz), 7.60 (1H, td, J = 8.0, 6.8 Hz), 7.77 (1H, d, J = 10.0 Hz), 7.87 (1H, d, J = 8.0 Hz), 8.02 (1H, d, J = 8.0 Hz), 8.49 (1H, d, J = 8.0 Hz), 14.32 (1H, s).

PRODUCTION EXAMPLE I-2-b

3-(3-Fluorophenyl)-1*H*-7-indazolecarboxylic acid

A total of 637 mg of the title compound as yellow crystals was obtained from 593 mg of 3-(3-fluorophenyl)-1*H*-7-indazolecarbonitrile by the procedure of Production Example I-1-c.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.28 (1H, td, J = 8.0, 2.8 Hz), 7.36 (1H, dd, J = 7.2, 8.0 Hz), 7.60 (1H, td, J = 8.0, 6.8 Hz), 7.76 (1H, dd, J = 10.0, 2.8 Hz), 7.87 (1H, d, J = 8.0 Hz), 8.05 (1H, d, J = 8.0 Hz), 8.39 (1H, d, J = 8.0 Hz), 13.40 (1H, s), 13.43 (1H, s).

PRODUCTION EXAMPLE I-3-a

3-Fluoro-2-(1,1,1-trimethylsilyl)benzonitrile

To a solution of 5.57 g of *N,N*-diisopropylamine in 100 ml tetrahydrofuran at -30°C in an atmosphere of nitrogen gas was added 33 ml of 1.59 M solution of n-butyllithium in hexane, and the mixture was stirred at the same temperature for 25 minutes. After cooling to -78°C, a solution of 6.06 g of 3-fluorobenzonitrile in 9 ml tetrahydrofuran was added dropwise. After stirring at the same temperature for 1 hour, 12.7 ml of chlorotrimethylsilane was added dropwise. After stirring at the same temperature for 1 hour, saturated aqueous ammonium chloride solution was added and the solvent was removed. The residue was added with 130 ml of ethyl acetate, and sequentially washed with water and brine, and dried over anhydrous magnesium sulfate. After filtrating the organic layer through a silica pat, the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (hexane), to give 6.93 g of the title compound as a pale blue oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.48 (9H, s), 7.21 (1H, ddd, J = 1.2, 8.4, 9.2 Hz), 7.42 (1H, ddd, J = 5.6, 7.6, 8.4 Hz), 7.50 (1H, dd, J = 1.2, 7.6 Hz).

PRODUCTION EXAMPLE I-3-b

3-Fluoro-4-[(3-fluorophenyl)(hydroxy)methyl]-2-(1,1,1-trimethylsilyl)benzonitrile

In an atmosphere of nitrogen gas, 7.0 ml of 1.56 M n-butyllithium in hexane was added to a solution of 1.61 g of 2,2,6,6-tetramethylpiperidine in 20 ml tetrahydrofuran

under ice-cooling, and the mixture was stirred at the same temperature for 1 hour. After cooling to -78°C, a solution of 2.0 g of 3-fluoro-2-(1,1,1-trimethylsilyl)benzonitrile in 5 ml tetrahydrofuran was added dropwise. After stirring at the same temperature for 55 minutes, 1.10 ml of 3-fluorobenzaldehyde was added dropwise. After stirring at the same temperature for 1 hour, 1.5 ml of glacial acetic acid was added and the mixture was returned to room temperature. After adding 40 ml of water, the mixture was extracted with diethyl ether. The organic layer was sequentially washed with 1 N hydrochloric acid, water, saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:9), to give 1.35 g of the title compound as a pale yellow viscous oil.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 0.40 (9H, s), 5.97 (1H, d, J = 4.0 Hz), 6.35 (1H, d, J = 4.0 Hz), 7.08 (1H, td, J = 8.0, 2.8 Hz), 7.15 (1H, d, J = 8.0 Hz), 7.17 (1H, dd, J = 8.0, 2.8 Hz), 7.37 (1H, td, J = 8.0, 6.0 Hz), 7.72 (1H, d, J = 8.0 Hz), 7.76 (1H, t, J = 8.0 Hz).

PRODUCTION EXAMPLE I-3-c

3-(3-Fluorophenyl)-1*H*-6-indazolecarbonitrile

To a solution of 1.35 g of 3-fluoro-4-[(3-fluorophenyl)(hydroxy)methyl]-2-(1,1,1-trimethylsilyl)benzonitrile in 30 ml methylene chloride was

added 4.5 g of activated manganese dioxide, the mixture was stirred at room temperature for five days, and then the manganese dioxide was filtered off through Celite. After removing the solvent by distillation, the residue was dissolved in 5 ml of tetrahydrofuran and 5 ml of methanol, 1.0 ml of hydrazine monohydrate was added and the mixture was stirred at room temperature for 1 day. The reaction mixture was added with water and extracted with ethyl acetate. The organic layer was sequentially washed with water and brine, dried over anhydrous magnesium sulfate and the solvent was removed. Then, the resulting crystals were suspended in diisopropyl ether, to give 62 mg of the title compound as pale yellow crystals. After concentrating the mother liquor, the residue was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 1:9), to give 30 mg of the title compound as yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.29 (1H, td, J = 8.0, 2.8 Hz), 7.54 (1H, dd, J = 8.4, 1.2 Hz), 7.59 (1H, td, J = 8.0, 6.4 Hz), 7.77 (1H, dd, J = 10.4, 2.8 Hz), 7.86 (1H, d, J = 8.0 Hz), 8.26 (1H, s), 8.31 (1H, d, J = 8.4 Hz), 13.96 (1H, s).

PRODUCTION EXAMPLE I-3-d

3-(3-Fluorophenyl)-1*H*-6-indazolecarboxylic acid

To 92 mg of 3-(3-fluorophenyl)-1*H*-6-indazolecarbonitrile were sequentially added 1 ml of glacial acetic acid, 0.5 ml of water and 0.4 ml of

concentrated sulfuric acid, and the mixture was stirred at 110°C for 6 hours. After standing to cool, 35 ml of ethyl acetate was added to the reaction mixture. The mixture was sequentially washed with water and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 94 mg of the title compound as bright yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.27 (1H, td, J = 8.4, 2.4 Hz), 7.59 (1H, td, J = 8.0, 6.4 Hz), 7.74-7.81 (2H, m), 7.88 (1H, d, J = 8.0 Hz), 8.19 (1H, s), 8.20 (1H, d, J = 9.6 Hz), 8.65 (1H, s), 13.14 (1H, s), 13.71 (1H, s).

PRODUCTION EXAMPLE I-4-a

[5-(Dimethoxymethyl)-2-fluorophenyl](3-fluorophenyl)methanol

A total of 21.6 g of 3-bromo-4-fluorobenzaldehyde was dissolved in a mixture of 50 ml of methyl orthoformate and 50 ml of methanol, and 0.2 g of p-toluenesulfonic acid monohydrate was added, followed by stirring at room temperature for 1 hour. To the reaction mixture was added aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 24.3 g of 3-bromo-4-fluorobenzaldehyde dimethylacetal as a colorless oil. The product was dissolved in 150 ml of dry tetrahydrofuran. After cooling to -78°C in an atmosphere of nitrogen gas, 59

ml of a 2.5 M solution of n-butyllithium in hexane was added. After stirring for 30 minutes, 12.7 ml of 3-fluorobenzaldehyde was added and the mixture was heated to room temperature. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate for two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:15), to give 24.3 g of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.20 (3H, s), 3.31 (3H, s), 5.36 (1H, s), 5.93 (1H, d, J = 4.4 Hz), 6.19 (1H, d, J = 4.4 Hz), 7.00-7.07 (1H, m), 7.07-7.15 (3H, m), 7.25-7.30 (1H, m), 7.30-7.38 (1H, m), 7.56 (1H, dd, J = 2.8, 7.4 Hz).

PRODUCTION EXAMPLE I-4-b

[5-(Dimethoxymethyl)-2-fluorophenyl](3-fluorophenyl)methanone

In a mixture of 80 ml of dichloromethane and 80 ml of dimethylsulfoxide were dissolved 24.3 g of [5-(dimethoxymethyl)-2-fluorophenyl](3-fluorophenyl)methanol and 27.6 ml of triethylamine, and a suspension of 26.3 g of sulfur trioxide-pyridine complex in 30 ml dimethyl sulfoxide was added, followed by stirring at room temperature for 1 hour. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate for

two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:15), to give 18.7 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.25 (6H, s), 5.45 (1H, s), 7.40 (1H, dd, J = 8.8, 10.5 Hz), 7.51-7.63 (5H, m), 7.63-7.69 (1H, m).

PRODUCTION EXAMPLE I-4-c

The title compound was also synthetically prepared by another procedure as mentioned below. A total of 2.0 g of [5-(dimethoxymethyl)-2-fluorophenyl](3-fluorophenyl)methanol was dissolved in 20 ml of dichloromethane, and the solution was treated with 5 g of manganese dioxide with stirring at room temperature for one day. The reaction mixture was filtrated using a Celite, the solvent was removed by distillation under reduced pressure, to give 2.0 g of the title compound.

PRODUCTION EXAMPLE I-4-d

Methyl 4-fluoro-3-(3-fluorobenzoyl)benzoate

A total of 18.7 g of [5-(dimethoxymethyl)-2-fluorophenyl](3-fluorophenyl)methanone was dissolved in 100 ml of tetrahydrofuran, and 5 ml of 5 N hydrochloric acid was added, followed by stirring at room temperature for 1 hour. To the reaction mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was

extracted with ethyl acetate for two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 15.8 g of 4-fluoro-3-(3-fluorobenzoyl)benzaldehyde as a colorless oil. A total of 13.8 g of this compound was dissolved in 50 ml of dimethyl sulfoxide, and a solution of 15.2 g of sodium chlorite in 50 ml water was added dropwise over 1 hour under ice-cooling. To the reaction mixture was added diluted hydrochloric acid, and the mixture was extracted with ethyl acetate for two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was filtered using diisopropyl ether, to give 12.9 g of 4-fluoro-3-(3-fluorobenzoyl)benzoic acid as a colorless solid. A total of 11.1 g of this compound was dissolved in 50 ml of N,N-dimethylformamide, and 5.8 g of potassium carbonate and 2.9 ml of methyl iodide were added, followed by stirring at room temperature for 12 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate for two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:15), to give 11.5 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.93 (3H, s), 7.25 (1H, t, J = 9.2 Hz), 7.32

(1H, ddt, J = 1.2, 2.7, 8.0 Hz), 7.46 (1H, dt, J = 5.3, 8.0 Hz), 7.50-7.59 (2H, m), 8.21-8.26 (2H, m).

PRODUCTION EXAMPLE I-4-e

Methyl 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylate

A total of 11.5 g of methyl 4-fluoro-3-(3-fluorobenzoyl)benzoate was dissolved in 40 ml of ethanol, and the reaction mixture as treated with 2.4 ml of hydrazine monohydrate with stirring at room temperature for 12 hours. The reaction mixture was treated with 2 N hydrochloric acid to be acidic and was extracted with two portions of ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was recrystallized from hexane-diisopropyl ether, to give 7.0 g of title compound as colorless crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.96 (3H, s), 7.15 (1H, t, J = 8.3 Hz), 7.48-7.55 (2H, m), 7.70 (1H, d, J = 10.0 Hz), 7.79 (1H, d, J = 8.8 Hz), 8.12 (1H, d, J = 8.8 Hz), 8.77 (1H, s).

PRODUCTION EXAMPLE I-4-f

3-(3-Fluorophenyl)-1*H*-5-indazolecarboxylic acid

A total of 2.1 g of the title compound as a colorless powder was obtained by the procedure of Production Example I-5-b, except from 2.7 g of methyl 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylate.

The ^{1}H-NMR spectrum thereof agrees with that of the compound according to Production Example I-1-c.

PRODUCTION EXAMPLE I-5-a

Methyl 3-(2-fluorophenyl)-1*H*-5-indazolecarboxylate

A total of 1.9 g of the title compound was obtained as a colorless powder by the procedures of Production Examples I-4-a, I-4-c, I-4-d, and I-4-e, except from 3.7 g of 3-bromo-4-fluorobenzaldehyde dimethylacetal produced in Production Example I-4-a and 1.73 ml of 2-fluorobenzaldehyde as starting materials.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.95 (3H, s), 7.26-7.32 (1H, m), 7.32 (1H, dt, J = 1.7, 7.4 Hz), 7.44-7.51 (1H, m), 7.53 (1H, d, J = 8.7 Hz), 7.82 (1H, dt, J = 1.7, 7.4 Hz), 8.13 (1H, dd, J = 1.6, 8.7 Hz), 8.64(1H, bs).

PRODUCTION EXAMPLE I-5-b

3-(2-Fluorophenyl)-1*H*-5-indazolecarboxylic acid

A total of 1.6 g of methyl 3-(2-fluorophenyl)-1*H*-5-indazolecarboxylate was dissolved in 15 ml of a 1:1 solvent mixture of methanol and tetrahydrofuran, 2 ml of 5 N aqueous sodium hydroxide solution was added, followed by heating at 70°C for 6 hours. After cooling to room temperature, the reaction mixture was added with diluted hydrochloric acid and was extracted with ethyl acetate for two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 1.5 g of the title compound as a colorless powder.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.38 (1H, dt, J = 1.2, 7.5 Hz), 7.43 (1H,

ddd, J = 1.2, 8.3, 10.9 Hz), 7.50-7.57 (1H, m), 7.66 (1H, d, J = 8.7 Hz), 7.80 (1H, dd, J = 1.9, 7.5 Hz), 7.95 (1H, dd, J = 1.2, 8.7 Hz), 8.39 (1H, bs), 13.71 (1H, s).

PRODUCTION EXAMPLE I-6-a

Methyl 3-(2-pyridyl)-1*H*-5-indazolecarboxylate

A total of 1.0 g of the title compound was obtained as a colorless powder by the procedures of Production Examples I-4-a, I-4-c, I-4-d, and I-4-e, except from 3.7 g of 3-bromo-4-fluorobenzaldehyde dimethylacetal produced in Production Example I-4-a and 1.6 ml of 2-pyridinecarboxaldehyde as starting materials.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, s), 7.31 (1H, ddd, J = 1.8, 5.2, 7.8 Hz), 7.54 (1H, d, J = 8.6 Hz), 7.82 (1H, dt, J = 1.8, 7.8 Hz), 8.13 (1H, dd, J = 1.8, 8.6 Hz), 8.19 (1H, d, J = 7.8 Hz), 8.81 (1H, dd, J = 1.8, 5.2 Hz), 9.42 (1H, d, J = 1.8 Hz).

PRODUCTION EXAMPLE I-6-b

3-(2-Pyridyl)-1*H*-5-indazolecarboxylic acid

A total of 0.8 g of the title compound was obtained as a pale yellow powder by the procedure of Production Example I-5-b, except from 1.0 g of methyl 3-(2-pyridyl)-1*H*-5-indazolecarboxylate.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, ddd, J = 1.8, 4.6, 7.5 Hz), 7.64 (1H, d, J = 8.5 Hz), 7.91 (1H, dt, J = 1.8, 7.5 Hz), 7.95 (1H, dd, J = 1.8, 8.5 Hz), 8.18 (1H, d, J = 8.5 Hz), 8.77 (1H, dd, J = 1.8, 4.6 Hz), 9.25 (1H, s), 13.63 (1H, bs).

PRODUCTION EXAMPLE I-7-a

Methyl 3-(3-pyridyl)-1*H*-5-indazolecarboxylate

A total of 0.88 g of the title compound was obtained as a colorless powder by the procedures of Production Examples I-4-a, I-4-c, I-4-d, and I-4-e, except from 6.5 g of 3-bromo-4-fluorobenzaldehyde dimethylacetal produced in Production Example I-4-a and 2.7 ml of 3-pyridinecarboxaldehyde as starting materials.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.96 (3H, s), 7.49 (1H, dd, J = 5.1, 7.6 Hz), 7.57 (1H, d, J = 9.1 Hz), 8.15 (1H, dd, J = 1.0, 9.1 Hz), 8.30 (1H, dt, J = 2.0, 7.6 Hz), 8.71 (1H, dd, J = 2.0, 5.1 Hz), 8.78 (1H, d, J = 1.0 Hz), 9.18 (1H, d, J = 2.0 Hz).

PRODUCTION EXAMPLE I-7-b

3-(3-Pyridyl)-1*H*-5-indazolecarboxylic acid

A total of 0.66 g of the title compound was obtained as a pale yellow powder by the procedure of Production Example I-5-b, except from 0.88 g of methyl 3-(3-pyridyl)-1*H*-5-indazolecarboxylate.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.58 (1H, dd, J = 5.2, 8.0 Hz), 7.68 (1H, d, J = 8.8 Hz), 7.98 (1H, dd, J = 1.5, 8.8 Hz), 8.34 (1H, dt, J = 1.9, 8.0 Hz), 8.62 (1H, s), 8.64 (1H, dd, J = 1.9, 5.2 Hz), 9.15 (1H, d, J = 1.9 Hz), 12.80-12.95 (1H, bs), 13.73 (1H, s).

PRODUCTION EXAMPLE I-8-a

Methyl 3-(2-methoxyphenyl)-1*H*-5-indazolecarboxylate

A total of 2.2 g of the title compound was obtained as a colorless oil by the procedures of Production Examples I-4-a, I-4-c, I-4-d, and I-4-e, except from 3.7 g of 3-bromo-

4-fluorobenzaldehyde dimethylacetal produced in Production Example I-4-a and 2.0 ml of o-anisaldehyde as starting materials.

^{1}H-NMR (400 MHz ,$CDCl_3$) δ 3.89 (3H, s), 3.93 (3H, s), 7.11 (1H, d, J = 8.3 Hz), 7.13 (1H, t, J = 7.5 Hz), 7.47 (1H, dt, J = 1.7, 8.7 Hz), 7.50 (1H, d, J = 8.3 Hz), 7.68 (1H, dd, J = 1.7, 7.5 Hz), 8.07 (1H, dd, J = 1.7, 8.7 Hz), 8.58 (1H, s).

PRODUCTION EXAMPLE I-8-b

3-(2-Methoxyphenyl)-1*H*-5-indazolecarboxylic acid

A total of 2.1 g of the title compound was obtained as a colorless powder by the procedure of Production Example I-5-b, except from 2.2 g of methyl 3-(2-methoxyphenyl)-1*H*-5-indazolecarboxylate.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.79 (3H, s), 7.07 (1H, dt, J = 1.2, 7.1 Hz), 7.20 (1H, d, J = 7.4 Hz), 7.46 (1H, ddd, J = 1.9, 7.1, 9.1 Hz), 7.53 (1H, d, J = 1.9, 7.4 Hz), 7.58 (1H, dd, J = 1.2, 9.1 Hz), 7.90 (1H, dd, J = 1.6, 9.1 Hz), 8.29 (1H, s), 13.35-13.50 (1H, bs).

PRODUCTION EXAMPLE I-9-a

Methyl 3-(2-quinolyl)-1*H*-5-indazolecarboxylate

A total of 1.3 g of the title compound was obtained as a colorless powder by the procedures of Production Examples I-4-a, I-4-c, I-4-d, and I-4-e, except from 3.7 g of 3-bromo-4-fluorobenzaldehyde dimethylacetal produced in Production Example I-4-a and 2.4 g of 2-quinolinecarboxaldehyde as starting materials.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.03 (3H, s), 7.57 (1H, d, J = 8.2 Hz), 7.59

(1H, dd, J = 1.8, 8.2 Hz), 7.78 (1H, dt, J = 1.8, 8.2 Hz), 7.86 (1H, d, J = 8.2 Hz), 8.17 (1H, dd, J = 1.8, 8.2 Hz), 8.27 (1H, d, J = 8.2 Hz), 8.33 (1H, d, J = 8.2 Hz), 8.35 (1H, d, J = 8.2 Hz), 9.62 (1H, s).

PRODUCTION EXAMPLE I-9-b

3-(2-Quinolyl)-1*H*-5-indazolecarboxylic acid

A total of 1.1 g of the title compound was obtained as a pale yellow powder by the procedure of Production Example I-5-b, except from 1.3 g of methyl 3-(2-quinolyl)-1*H*-5-indazolecarboxylate.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.62 (1H, ddd, J = 0.9, 6.9, 8.0 Hz), 7.69 (1H, dd, J = 0.9, 8.7 Hz), 7.82 (1H, ddd, J = 1.5, 6.9, 8.0 Hz), 8.00 (1H, dd, J = 1.8, 8.7 Hz), 8.01 (1H, d, J = 8.0 Hz), 8.11 (1H, d, J = 8.0 Hz), 8.35 (1H, d, J = 8.0 Hz), 8.46 (1H, d, J = 8.7 Hz), 9.53 (1H, s), 13.80 (1H, s).

PRODUCTION EXAMPLE I-10-a

Methyl 3-(3-quinolyl)-1*H*-5-indazolecarboxylate

A total of 2.1 g of the title compound was obtained as a pale yellow powder by the procedures of Production Examples I-4-a, I-4-c, I-4-d, and I-4-e, except from 4.98 g of 3-bromo-4-fluorobenzaldehyde dimethylacetal produced in Production Example I-4-a and 3.14 g of 3-quinolinecarboxaldehyde as starting materials.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.90 (3H, s), 7.68 (1H, t, J = 7.6 Hz), 7.74 (1H, d, J = 8.7 Hz), 7.81 (1H, t, J = 7.6 Hz), 8.02 (1H, dd, J = 1.6, 8.7 Hz), 8.08 (1H, d, J = 7.6 Hz), 8.22 (1H, d, J = 7.6 Hz), 8.80 (1H, s), 8.94 (1H, d, J = 2.3 Hz), 9.50 (1H, d, J = 2.3 Hz).

PRODUCTION EXAMPLE I-10-b

3-(3-Quinolyl)-1*H*-5-indazolecarboxylic acid

A total of 1.9 g of the title compound was obtained as a pale yellow powder by the procedure of Production Example I-5-b, except from 2.1 g of methyl 3-(3-quinolyl)-1*H*-5-indazolecarboxylate.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.65 (1H, t, J = 7.6 Hz), 7.68 (1H, d, J = 8.7 Hz), 7.80 (1H, t, J = 7.6 Hz), 8.02 (1H, dd, J = 1.4, 8.7 Hz), 8.22 (1H, d, J = 7.6 Hz), 8.22 (1H, d, J = 7.6 Hz), 8.77 (1H, s), 8.93 (1H, d, J = 2.3 Hz), 9.51 (1H, d, J = 2.3 Hz), 13.75-13.85 (1H, bs).

PRODUCTION EXAMPLE I-11-a

Methyl 3-(4-quinolyl)-1*H*-5-indazolecarboxylate

A total of 2.00 g of the title compound was obtained as a colorless powder by the procedures of Production Examples I-4-a, I-4-c, I-4-d, and I-4-e, except from 4.98 g of 3-bromo-4-fluorobenzaldehyde dimethylacetal produced in Production Example I-4-a and 3.14 g of 4-quinolinecarboxaldehyde as starting materials.

^{1}H-NMR (400 MHz, DMSO-d6) δ 3.83 (3H, s), 7.64 (1H, t, J = 7.6 Hz), 7.80 (1H, d, J = 9.2 Hz), 7.83 (1H, t, J = 7.6 Hz), 7.83 (1H, d, J = 4.3 Hz), 8.03 (1H, dd, J = 1.2, 9.2 Hz), 8.14 (1H, d, J = 7.6 Hz), 8.38 (1H, d, J = 1.2 Hz), 8.39 (1H, d, J = 7.6 Hz), 9.07 (1H, d, J = 4.3 Hz).

PRODUCTION EXAMPLE I-11-b

3-(4-Quinolyl)-1*H*-5-indazolecarboxylic acid

A total of 1.8 g of the title compound was obtained as

a pale yellow powder by the procedure of Production Example I-5-b, except from 2.0 g of methyl 3-(4-quinolyl)-1*H*-5-indazolecarboxylate.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.65 (1H, t, J = 7.5 Hz), 7.77 (1H, d, J = 8.7 Hz), 7.84 (1H, t, J = 7.5 Hz), 7.85 (1H, d, J = 4.4, Hz), 8.02 (1H, dd, J = 1.4, 8.7 Hz), 8.14 (1H, d, J = 7.6 Hz), 8.37 (1H, s), 8.43 (1H, d, J = 7.6 Hz), 9.08 (1H, d, J = 4.4 Hz), 14.00 (1H, s).

PRODUCTION EXAMPLE I-12-a

Methyl 3-(2-naphthyl)-1*H*-5-indazolecarboxylate

A total of 5.70 g of the title compound was obtained as a colorless powder by the procedures of Production Examples I-4-a, I-4-c, I-4-d, and I-4-e, except from 7.50 g of 3-bromo-4-fluorobenzaldehyde dimethylacetal produced in Production Example I-4-a and 5.20 g of 2-naphthylaldehyde as starting materials.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.88 (3H, s), 7.53-7.60 (2H, m), 7.71 (1H, dd, J = 0.9, 8.8 Hz), 7.96-7.99 (1H, m), 8.00 (1H, dd, J = 1.3, 8.8 Hz), 8.08 (1H, d, J = 8.8 Hz), 8.10-8.13 (m, 1H), 8.12 (1H, dd, J = 1.8, 8.8 Hz), 8.51 (bs, 1H), 8.78 (1H, dd, J = 0.9, 1.3 Hz).

PRODUCTION EXAMPLE I-12-b

3-(2-Naphthyl)-1*H*-5-indazolecarboxylic acid

A total of 0.9 g of the title compound was obtained as white crystals by the procedure of Production Example I-5-b, except from 1.0 g of methyl 3-(2-naphthyl)-1*H*-5-indazolecarboxylate.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.34-7.62 (2H, m), 7.70 (1H, d, J = 8.8

Hz), 7.96-8.04 (2H, m), 8.10 (1H, d, J = 8.8 Hz), 8.12-8.18 (2H, m), 8.55 (1H, s), 8.79 (1H, s), 12.92 (1H, s), 13.66 (1H, s).

PRODUCTION EXAMPLE I-13-a

5-(Dimethoxymethyl)-2-fluorobenzaldehyde

A total of 2.49 g of 3-bromo-4-fluorobenzaldehyde dimethylacetal produced in Production Example I-4-a was dissolved in 20 ml of dry tetrahydrofuran. After cooling to -78°C in an atmosphere of nitrogen gas, 8.5 ml of a 1.56 M solution of n-butyllithium in hexane was added. After stirring for 30 minutes, 1.0 ml of N,N-dimethylformamide was added and the mixture was heated to room temperature. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate for two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:12.5), to give 1.35 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.24 (6H, s), 5.45 (1H, s), 7.42 (1H, dd, J = 9.0, 10.0 Hz), 7.68-7.75 (1H, m), 7.82(1H, dd, J = 2.0, 7.0 Hz), 10.21(1H, s).

PRODUCTION EXAMPLE I-13-b

1,3-Benzothiazol-2-yl[5-(dimethoxymethyl)-2-fluorophenyl]methanol

A total of 1.08 g of benzothiazole was dissolved in 15

ml of dry tetrahydrofuran. After cooling to -78°C in an atmosphere of nitrogen gas, 6.4 ml of 1.56 M solution of n-butyllithium in hexane was added. After stirring for 5 minutes, 8 ml of a solution of 1.35 g of 5-(dimethoxymethyl)-2-fluorobenzaldehyde in dry tetrahydrofuran was added, followed by stirring for 10 minutes. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate for two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 3:7), to give 1.8 g of the title compound as a yellow oil.

^{1}H-NMR (400 MHz, DMSO-d6) δ 3.20 (6H, s), 5.35 (1H, s), 6.25 (1H, s), 7.11-7.16 (1H, bs), 7.21 (1H, dd, J = 8.2, 9.7 Hz), 7.32-7.37 (1H, m), 7.39 (1H, t, J = 7.7 Hz), 7.45 (1H, t, J = 7.7 Hz), 7.55 (1H, d, J = 2.6, 6.7 Hz), 7.88 (1H, d, J = 7.7 Hz), 8.08 (1H, d, J = 7.7 Hz).

PRODUCTION EXAMPLE I-13-c

Methyl 3-(1,3-benzothiazol-2-yl)-1*H*-5-indazolecarboxylate

A total of 1.05 g of the title compound was obtained as a colorless powder by the procedures of Production Examples I-4-c, I-4-d, and I-4-e, except from 1.8 g of 1,3-benzothiazol-2-yl[5-(dimethoxymethyl)-2-fluorophenyl]methanol as a starting material.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.02 (3H, s), 7.45 (1H, ddd, J = 1.1, 7.2,

142

8.4 Hz), 7.55 (1H, ddd, J = 1.1, 7.2, 8.4 Hz), 7.59 (1H, dd, J = 0.9, 8.9 Hz), 7.97 (1H, ddd, J = 0.7, 1.1, 8.1 Hz), 8.20 (1H, dd, J = 1.4, 8.9 Hz), 8.23 (1H, ddd, J = 0.7, 1.1, 8.1 Hz), 9.41 (1H, dd, J = 0.9, 1.4 Hz), 10.36-10.48 (1H, bs).

PRODUCTION EXAMPLE I-13-d

3-(1,3-Benzothiazol-2-yl)-1*H*-5-indazolecarboxylic acid

A total of 0.95 g of the title compound was obtained as a colorless powder by the procedure of Production Example I-5-b, except from 1.2 g of methyl 3-(1,3-benzothiazol-2-yl)-1*H*-5-indazolecarboxylate.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.39 (1H, t, J = 7.2 Hz), 7.57 (1H, t, J = 7.2 Hz), 7.75 (1H, dd, J = 0.8, 8.6 Hz), 8.04 (1H, dd, J = 1.8, 8.6 Hz), 8.16 (1H, d, J = 7.2 Hz), 8.19 (1H, d, J = 7.2 Hz), 9.14 (1H, dd, J = 0.8, 1.8 Hz), 12.80-13.20 (1H, bs), 14.07 (1H, s).

PRODUCTION EXAMPLE I-14-a

3-Bromo-1*H*-5-indazolecarbonitrile

To a solution of 300 mg of a compound 1*H*-5-indazolecarbonitrile (synthesized from 4-fluorobenzonitrile according to the procedures described in literature, Tetrahedron Lett., 33, 7499(1992) and Synthetic commun., 27, 1199(1997)) in 3 ml dimethylformamide was added 392 mg of N-bromosuccinimide at room temperature, and the mixture was stirred at the same temperature for one day. After removing the solvent by distillation, the residue was added with 25 ml of ethyl acetate. The mixture was sequentially washed with half-saturated aqueous sodium hydrogencarbonate

solution, water and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 440 mg of the title compound as pale red crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, dd, J = 8.4, 0.8 Hz), 7.67 (1H, dd, J = 8.4, 1.6 Hz), 8.07 (1H, dd, J = 1.6, 0.8 Hz).

PRODUCTION EXAMPLE I-14-b

tert-Butyl 3-bromo-5-cyano-1*H*-1-indazolecarboxylate

To a solution of 6.25 g of 3-bromo-1*H*-5-indazolecarbonitrile in 100 ml tetrahydrofuran at room temperature were added 6.76 g of di-*tert*-butyl dicarbonate and 516 mg of 4-(dimethylamino)pyridine, and the mixture was stirred at the same temperature overnight. After removing the solvent by distillation, the residue was added with 220 ml of ethyl acetate. The mixture was sequentially washed with diluted hydrochloric acid, water, saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 8.69 g of the title compound as pale red crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.73 (9H, s), 7.80 (1H, dd, J = 8.8, 1.6 Hz), 8.03 (1H, d, J = 1.6 Hz), 8.30 (1H, d, J = 8.8 Hz).

PRODUCTION EXAMPLE I-14-c

3-(4-Fluorophenyl)-1*H*-5-indazolecarbonitrile

To a solution of 2.0 g of *tert*-butyl 3-bromo-5-cyano-1*H*-1-indazolecarboxylate in 30 ml tetrahydrofuran were added 70 mg of palladium(II) acetate, 218 mg of 2-

(dicyclohexylphosphino)biphenyl, 1.19 g of potassium fluoride and 1.30 g of 4-fluorophenylboronic acid, and the mixture was stirred at 50°C for one day. After removing the solvent by distillation, the residue was diluted with 40 ml of ethyl acetate. The mixture was sequentially washed with water and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was dissolved in 25 ml of methylene chloride, and 5 ml of trifluoroacetic acid was added, followed by stirring at room temperature for 1 hour. After removing the solvent by distillation, the residue was diluted with 40 ml of ethyl acetate. The mixture was sequentially washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 1:19 to 1:9), to give 1.09 g of the title compound as bright yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.36 (2H, t, J = 8.8 Hz), 7.74 (1H, dd, J = 8.8, 1.2 Hz), 7.76 (1H, dd, J = 8.8, 1.2 Hz), 8.10 (2H, dd, J = 8.8, 5.6 Hz), 8.71 (1H, s), 13.78 (1H, s).

PRODUCTION EXAMPLE I-14-d

3-(4-Fluorophenyl)-1*H*-5-indazolecarboxylic acid

To 1.0 g of 3-(4-fluorophenyl)-1*H*-5-indazolecarbonitrile were added 5 ml of water, 4 ml of concentrated sulfuric acid and 4 ml of glacial acetic acid,

and the mixture was heated under reflux for 3 hours. After standing to cool, 25 ml of ice-cooled water was added. The resulting crystals were collected by filtration. The collected crystals were dissolved in 250 ml of ethyl acetate, sequentially washed with water and brine, and dried over anhydrous magnesium sulfate. After filtrating the organic layer through a silica gel pat, the solvent was evaporated, to give 968 mg of the title compound as bright yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.41 (2H, t, J = 8.8 Hz), 7.66 (1H, d, J = 8.8 Hz), 7.95-8.09 (3H, m), 8.63 (1H, s), 12.91 (1H, s), 13.58 (1H, s).

PRODUCTION EXAMPLE I-15-a

3-(3-Chlorophenyl)-1*H*-5-indazolecarbonitrile

A total of 137 mg of the title compound was obtained as white crystals by the procedure of Production Example I-14-c, except from 2.0 g of *tert*-butyl 3-bromo-5-cyano-1*H*-1-indazolecarboxylate produced in Production Example I-14-b and 1.46 g of 3-chlorophenylboronic acid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 (1H, dt, J = 8.0, 1.6 Hz), 7.51 (1H, d, J = 8.4 Hz), 7.64 (1H, t, J = 8.0 Hz), 7.67 (1H, dd, J = 8.4, 1.2 Hz), 7.81 (1H, dt, J = 8.0, 1.6 Hz), 7.93 (1H, t, J = 1.6 Hz), 8.40 (1H, d, J = 1.2 Hz).

PRODUCTION EXAMPLE I-15-b

3-(3-Chlorophenyl)-1*H*-5-indazolecarboxylic acid

A total of 115 mg of the title compound was obtained as beige crystals by the procedure of Production Example I-

14-d, except using 135 mg of 3-(3-chlorophenyl)-1*H*-5-indazolecarbonitrile.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.53 (1H, dd, J = 8.0, 1.6 Hz), 7.62 (1H, td, J = 8.0, 1.6 Hz), 7.69 (1H, d, J = 8.0 Hz), 7.93-8.05 (3H, m), 8.63 (1H, s), 12.90 (1H, s), 13.71 (1H, s).

PRODUCTION EXAMPLE I-16-a

3-[3-(Trifluoromethyl)phenyl]-1*H*-5-indazolecarbonitrile

A total of 58 mg of the title compound was obtained as white crystals by the procedure of Production Example I-14-c, except using 500 mg of *tert*-butyl 3-bromo-5-cyano-1*H*-1-indazolecarboxylate produced in Production Example I-14-b and 442 mg of 3-trifluoromethylphenylboronic acid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63-7.76 (4H, m), 8.11 (1H, d, J = 7.6 Hz), 8.21 (1H, s), 8.40 (1H, s).

PRODUCTION EXAMPLE I-16-b

3-[3-(Trifluoromethyl)phenyl]-1*H*-5-indazolecarboxylic acid

A total of 54 mg of the title compound was obtained as beige crystals by the procedure of Production Example I-14-d, except using 57 mg of 3-[3-(trifluoromethyl)phenyl]-1*H*-5-indazolecarbonitrile.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.71 (1H, d, J = 8.4 Hz), 7.83 (2H, m), 8.01 (1H, d, J = 8.8 Hz), 8.24 (1H, s), 8.32 (1H, m), 8.66 (1H, s), 12.96 (1H, s), 13.77 (1H, s).

PRODUCTION EXAMPLE I-17-a

3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolecarbonitrile

To a solution of 600 mg of *tert*-butyl 3-bromo-5-cyano-

1*H*-1-indazolecarboxylate produced in Production Example I-14-b in 9 ml tetrahydrofuran were added 21 mg of palladium(II) acetate, 57 mg of 2-(di-*tert*-butylphosphino)biphenyl, 357 mg of potassium fluoride and 498 mg of 2-benzo[*b*]thiopheneboronic acid, and the mixture was stirred at 50°C for 1 hour. After removing the solvent by distillation, the residue was dissolved in 2 ml of methylene chloride. 4 ml of trifluoroacetic acid was added and the mixture was stirred at room temperature for one day. After removing the solvent by distillation, the residue was diluted with 50 ml of ethyl acetate. The mixture was sequentially washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 1:19), to give 294 mg of the title compound as bright yellow crystals.
^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.41 (2H, t, J = 7.8 Hz), 7.44 (2H, t, J = 7.8 Hz), 7.80 (2H, s), 7.91 (1H, d, J = 8.0 Hz), 8.01 (1H, d, J = 8.0 Hz), 8.41 (1H, s), 8.99 (1H, s), 13.88 (1H, s).

PRODUCTION EXAMPLE I-17-b

3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolecarboxylic acid

To 288 mg of 3-benzo[*b*]thiophen-2-yl-1*H*-5-indazolecarbonitrile were added 3 ml of glacial acetic acid, 1 ml of water and 0.8 ml of concentrated sulfuric acid, and the mixture was stirred at 110°C for 4 hours. After

standing to cool, the mixture was added with 120 ml of ethyl acetate, sequentially washed with water and brine, dried over anhydrous magnesium sulfate. After filtering the organic layer through a silica gel pat, the solvent was evaporated, to give 307 mg of the title compound as ocher yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.36-7.48 (2H, m), 7.71 (1H, d, J = 8.8 Hz), 7.99-8.07 (3H, m), 8.17 (1H, s), 8.83 (1H, s), 13.72 (1H, s).

PRODUCTION EXAMPLE I-18-a

3-(3-Methoxyphenyl)-1*H*-5-indazolecarbonitrile

A total of 66 mg of the title compound was obtained as bright yellow crystals by the procedure of Production Example I-17-a, except from 200 mg of *tert*-butyl 3-bromo-5-cyano-1*H*-1-indazolecarboxylate produced in Production Example I-14-b and 142 mg of 3-methoxyphenylboronic acid.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.87 (3H, s), 7.03 (1H, dd, J = 8.0, 2.4 Hz), 7.46 (1H, t, J = 8.0 Hz), 7.51 (1H, s), 7.62 (1H, d, J = 8.0 Hz), 7.73 (1H, d, J = 8.8 Hz), 7.77(1H, d, J = 8.8 Hz), 8.67 (1H, s), 13.76 (1H, s).

PRODUCTION EXAMPLE I-18-b

3-(3-Methoxyphenyl)-1*H*-5-indazolecarboxylic acid

A total of 14 mg of the title compound was obtained as orange crystals by the procedure of Production Example I-17-b, except from 65 mg of 3-(3-methoxyphenyl)-1*H*-5-indazolecarbonitrile.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.86 (3H, s), 7.04 (1H, dd, J = 8.4, 2.4

Hz), 7.50 (1H, t, J = 8.0 Hz), 7.54 (1H, s), 7.61 (1H, d, J = 8.0 Hz), 7.66 (1H, d, J = 8.0 Hz), 7.93(1H, d, J = 8.4 Hz), 8.60 (1H, s), 12.85 (1H, s), 13.44 (1H, s).

PRODUCTION EXAMPLE I-19-a

3-Benzo[*b*]thiophen-3-yl-1*H*-5-indazolecarbonitrile

A total of 303 mg of the title compound was obtained as light brown crystals by the procedure of Production Example I-17-a, except from 500 mg of *tert*-butyl 3-bromo-5-cyano-1*H*-1-indazolecarboxylate produced in Production Example I-14-b and 415 mg of 3-benzo[*b*]thiopheneboronic acid.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.45-7.55 (2H, m), 7.77 (1H, d, J = 8.8 Hz), 7.82 (1H, d, J = 8.8 Hz), 8.11 (1H, d, J = 7.2 Hz), 8.60 (1H, s), 8.70 (1H, d, J = 7.2 Hz), 8.77 (1H, s), 13.85 (1H, s).

PRODUCTION EXAMPLE I-19-b

3-Benzo[*b*]thiophen-3-yl-1*H*-5-indazolecarboxylic acid

A total of 301 mg of the title compound was obtained as red crystals by the procedure of Production Example I-17-b, except from 300 mg of 3-benzo[*b*]thiophen-3-yl-1*H*-5-indazolecarbonitile.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.45-7.55 (2H, m), 7.71 (1H, d, J = 8.8 Hz), 8.01 (1H, d, J = 8.8 Hz), 8.11 (1H, d, J = 7.2 Hz), 8.40 (1H, s), 8.57 (1H, d, J = 7.2 Hz), 8.66 (1H, s), 12.89 (1H, s), 13.65 (1H, s).

PRODUCTION EXAMPLE I-20-a

3-(5-Acetyl-2-thienyl)-1*H*-5-indazolecarbonitrile

A total of 94 mg of the title compound was obtained as

green crystals by the procedure of Production Example I-17-a, except from 500 mg of *tert*-butyl 3-bromo-5-cyano-1*H*-1-indazolecarboxylate produced in Production Example I-14-b and 528 mg of 5-acetyl-2-thiopheneboronic acid.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 2.59 (3H, s), 7.78 (1H, d, J = 8.8 Hz), 7.81 (1H, d, J = 8.8 Hz), 8.03 (1H, d, J = 4.0 Hz), 8.08 (1H, d, J = 4.0 Hz), 8.87 (1H, s), 13.98 (1H, s).

PRODUCTION EXAMPLE I-20-b

3-(5-Acetyl-2-thienyl)-1*H*-5-indazolecarboxylic acid

A total of 85 mg of the title compound was obtained as ocher yellow crystals by the procedure of Production Example I-17-b, except from 94 mg of 3-(5-acetyl-2-thienyl)-1*H*-5-indazclecarbonitrile.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 2.59 (3H, s), 7.70 (1H, d, J = 8.8 Hz), 7.87 (1H, d, J = 3.6 Hz), 8.01 (1H, d, J = 8.8 Hz), 8.03 (1H, d, J = 3.6 Hz), 8.69 (1H, s), 13.00 (1H, s), 13.82 (1H, s).

PRODUCTION EXAMPLE I-21-a

1*H*-5-Indazolecarboxylic acid

To 867 mg of 1*H*-5-indazolecarbonitrile used in Production Example I-14-a were added 8 ml of glacial acetic acid, 2.5 ml of water and 2 ml of concentrated sulfuric acid, and the mixture was stirred at 110°C for 10 hours. After standing to cool, the mixture was added with 50 ml of water, and the resulting crystals were collected by filtration and dried in vacuo, to give 911 mg of the title compound as white crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.59 (1H, dd, J = 0.8, 8.8 Hz), 7.91 (1H, dd, J = 0.8, 8.8 Hz), 8.24 (1H, s), 8.45 (1H, s), 13.36 (1H, s).

PRODUCTION EXAMPLE I-21-b

Methyl 1*H*-5-Indazolecarboxylate

Under ice-cooling, to a solution of 910 mg of 1*H*-5-indazolecarboxylic acid in 60 ml tetrahydrofuran was added an excess amount of a solution of diazomethane in diethyl ether, and the mixture was stirred at the same temperature for 1 hour. After removing the solvent by distillation, the residue was added with 50 ml of ethyl acetate, sequentially washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 923 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.87 (3H, s), 7.62 (1H, d, J = 8.8 Hz), 7.92 (1H, d, J = 8.8 Hz), 8.26 (1H, s), 8.49 (1H, s), 13.42 (1H, s).

PRODUCTION EXAMPLE I-21-c

1-(*tert*-Butyl) 5-methyl 3-bromo-1*H*-1,5-indazoledicarboxylate

A total of 1.43 g of the title compound was obtained as white crystals by the procedure of Production Examples I-14-a and I-14-b, except from 923 mg of methyl 1*H*-5-indazolecarboxylate.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.92 (3H, s), 8.19-8.24 (2H, m), 8.26 (1H, dd, J = 1.2, 8.8 Hz).

PRODUCTION EXAMPLE I-21-d

Methyl 3-benzo[*b*]furan-2-yl-1*H*-5-indazolecarboxylate

A total of 281 mg of the title compound was obtained by the procedure of Production Example I-17-a, except from 700 mg of 1-(*tert*-butyl) 5-methyl 3-bromo-1*H*-1,5-indazoledicarboxylate and 479 mg of 2-benzo[*b*]furanboronic acid.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.93 (3H, s), 7.33 (1H, t, J = 7.6 Hz), 7.40 (1H, t, J = 8.0 Hz), 7.56 (1H, s), 7.72-7.80 (3H, m), 8.03 (1H, dd, J = 1.6, 8.8 Hz), 8.86 (1H, s), 13.91 (1H, s).

PRODUCTION EXAMPLE I-21-e

3-Benzo[*b*]furan-2-yl-1*H*-5-indazolecarboxylic acid

To a solution of 275 mg of methyl 3-benzo[*b*]furan-2-yl-1*H*-5-indazolecarboxylate in 3 ml methanol and 3 ml tetrahydrofuran was added 1.5 ml of 5 N aqueous sodium hydroxide solution, and the mixture was stirred at room temperature for five days. After removing the solvent by distillation, the residue was added with 9 ml of 1 N hydrochloric acid, and the mixture was extracted with 200 ml of ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 320 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.32 (1H, t, J = 7.2 Hz), 7.39 (1H, t, J = 8.0 Hz), 7.54 (1H, s), 7.71 (1H, d, J = 8.8 Hz), 7.84-7.79 (2H, m), 8.02 (1H, d, J = 8.8 Hz), 8.85 (1H, s), 12.99 (1H, s), 13.85 (1H, s).

PRODUCTION EXAMPLE I-22-a

Methyl 3-(3-acetylphenyl)-1*H*-5-indazolecarboxylate

A total of 92 mg of the title compound was obtained as light brown crystals by the procedure of Production Example I-17-a, except from 355 mg of 1-(*tert*-butyl) 5-methyl 3-bromo-1*H*-1,5-indazoledicarboxylate produced in Production Example I-21-c and 246 mg of 3-acetylphenylboronic acid.

^{1}H-NMR (400 MHz, DMSO-D$_6$) δ 2.69 (3H, s), 3.90 (3H, s), 7.73 (1H, d, J = 8.8 Hz), 7.75 (1H, t, J = 8.0 Hz), 8.01 (1H, dd, J = 1.2, 8.8 Hz), 8.06 (1H, dt, J = 8.0, 1.2 Hz), 8.25 (1H, dt, J = 8.0, 1.2 Hz), 8.50 (1H, t, J = 1.2 Hz), 8.68 (1H, d, J = 1.2 Hz), 13.75 (1H, s).

PRODUCTION EXAMPLE I-22-b

3-(3-Acetylphenyl)-1*H*-5-indazolecarboxylic acid

A total of 83 mg of the title compound was obtained as yellow crystals by the procedure of Production Example I-21-e, except from 91 mg of methyl 3-(3-acetylphenyl)-1*H*-5-indazolecarboxylate.

^{1}H-NMR (400 MHz, DMSO-D$_6$) δ 2.68 (3H, s), 7.70 (1H, d, J = 8.8 Hz), 7.74 (1H, t, J = 8.0 Hz), 7.99 (1H, d, J = 8.8 Hz), 8.06 (1H, d, J = 8.0 Hz), 8.25 (1H, d, J = 8.0 Hz), 8.50 (1H, s), 8.68 (1H, s), 12.93 (1H, s), 13.70 (1H, s).

PRODUCTION EXAMPLE I-23-a

3-Phenyl-1*H*-5-indazolecarbonitrile

To a solution of 300 mg of *tert*-butyl 3-bromo-5-cyano-1*H*-1-indazolecarboxylate produced in Production Example I-14-b in 10 ml dimethylformamide were added 376 mg of tri-n-butyl(phenyl)tin and 54 mg of

tetrakis(triphenylphosphine)palladium(0), and the mixture was stirred at 150°C for 45 minutes. After removing the solvent by distillation, the residue was dissolved in 1.5 ml of ethyl acetate and the mixture was adsorbed by 1.5 g of silica gel. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 3:97 to 1:19) and the resulting amorphous powder was crystallized from diisopropyl ether, to give 117 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.46 (1H, t, J = 8.0 Hz), 7.55 (2H, t, J = 8.0 Hz), 7.73 (1H, d, J = 8.8 Hz), 7.77 (1H, d, J = 8.8 Hz), 8.05 (2H, d, J = 8.0 Hz), 8.71 (1H, s), 13.76 (1H, s).

PRODUCTION EXAMPLE I-23-b

3-Phenyl-1*H*-5-indazolecarboxylic acid

A total of 110 mg of the title compound was obtained as pale red crystals by the procedure of Production Example I-17-b, except from 116 mg of 3-phenyl-1*H*-5-indazolecarbonitrile.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.46 (1H, t, J = 8.0 Hz), 7.57 (2H, t, J = 8.0 Hz), 7.66 (1H, d, J = 8.8 Hz), 7.97 (3H, d, J = 8.0 Hz), 8.65 (1H, s), 12.10 (1H, s), 13.56 (1H, s).

PRODUCTION EXAMPLE I-24-a

tert-Butyl 3-(3-fluorophenyl)-5-(hydroxymethyl)-1*H*-1-indazolecarboxylate

Under ice-cooling, a solution of 10.66 g of 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylic acid produced in

Example I-1-c in 270 ml tetrahydrofuran was added 2.96 g of lithium aluminium hydride, and the mixture was stirred at the same temperature for 30 minutes and then heated under reflux for 7 hours. After ice-cooling again, 0.99 g of lithium aluminium hydride was further added, and the mixture was further heated under reflux for 2 hours. The reaction mixture was ice-cooled, and saturated aqueous ammonium chloride solution was added. Then, 200 ml of 1 N hydrochloric acid was added, and the mixture was extracted with ethyl acetate for two times. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. After filtrating the organic layer through a silica gel pat, the solvent was evaporated. After the resulting crystals were dissolved in 70 ml of tetrahydrofuran, 7.9 g of di-tert-butyl dicarbonate and 0.44 g of 4-N,N-dimethylaminopyridine were added and the mixture was stirred at room temperature for 1 hour. The reaction mixture was added with 250 ml of ethyl acetate, sequentially washed with 1 N hydrochloric acid, water, saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was removed. The residue was recrystallized from ethyl acetate-diisopropyl ether, to give 7.44 g of the title compound as white needles. The mother liquor was concentrated, and the residue was purified and separated by silica gel column chromatography (ethyl acetate:toluene =

156

1:9), to give 1.82 g of the title compound as yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 1.68 (9H, s), 4.68 (2H, d, J = 5.6 Hz), 5.38 (1H, t, J = 5.6 Hz), 7.41 (1H, td, J = 8.4, 2.4 Hz), 7.60-7.70 (2H, m), 7.75(1H, d, J = 9.2 Hz), 7.85 (1H, d, J = 8.0 Hz), 8.04 (1H, s), 8.12 (1H, d, J = 8.8 Hz).

PRODUCTION EXAMPLE I-24-b

tert-Butyl 5-(chloromethyl)-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate

Under ice-cooling, to a solution of 3.0 g of *tert*-butyl 3-(3-fluorophenyl)-5-(hydroxymethyl)-1*H*-1-indazolecarboxylate in 30 ml methylene chloride were added 1.6 ml of triethylamine and 0.78 ml of methanesulfonyl chloride, and the mixture was stirred at room temperature for one day. To the reaction mixture was added 180 ml of ethyl acetate, and the mixture was sequentially washed with water, 1 N hydrochloric acid, water, saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (toluene), to give 2.74 g of the title compound as yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 1.69 (9H, s), 4.99 (2H, s), 7.42 (1H, td, J = 8.0, 2.4 Hz), 7.67 (1H, td, J = 8.0, 6.4 Hz), 7.76 (1H, d, J = 8.8 Hz), 7.78 (1H, d, J = 8.0 Hz), 7.86 (1H, d, J = 8.0Hz), 8.18 (1H, d, J = 8.8 Hz), 8.27 (1H, s).

PRODUCTION EXAMPLE I-24-c

2-[3-(3-Fluorophenyl)-1*H*-5-indazolyl]acetonitrile

To a solution of 1.0 g of *tert*-butyl 5-(chloromethyl)-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate in 5 ml dimethyl sulfoxide was added 204 mg of sodium cyanide, and the mixture was stirred at room temperature for 50 minutes. To the reaction mixture was added 50 ml of ethyl acetate, and after washing with water, the aqueous layer was re-extracted with diethyl ether. The collected organic layer was sequentially washed with water (x2) and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 1:9), and suspended in diethyl ether-diisopropyl ether, to give 62 mg of the title compound as yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 4.16 (2H, s), 7.26 (1H, td, J = 8.4, 2.4 Hz), 7.42 (1H, d, J = 8.8 Hz), 7.59 (1H, td, J = 8.0, 6.4 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.74(1H, d, J = 10.4 Hz), 7.84 (1H, d, J = 8.0 Hz), 8.12 (1H, s), 13.46 (1H, s).

PRODUCTION EXAMPLE I-24-d

2-[3-(3-Fluorophenyl)-1*H*-5-indazolyl]acetic acid

50 mg of 2-[3-(3-fluorophenyl)-1*H*-5-indazolyl]acetonitrile was suspended in 0.5 ml of water and 0.4 ml of concentrated sulfuric acid, and the suspension was stirred at 95°C for 2 hours. The reaction mixture was added with 20 ml of ethyl acetate, sequentially washed with

water (x2) and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 48 mg of the title compound as pale red crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.74 (2H, s), 7.24 (1H, td, J = 8.4, 2.4 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.52-7.62 (2H, m), 7.74(1H, d, J = 10.4 Hz), 7.85 (1H, d, J = 8.0 Hz), 7.99 (1H, s), 12.31 (1H, s), 13.33 (1H, s).

PRODUCTION EXAMPLE I-25-a

tert-Butyl 3-(3-fluorophenyl)-5-formyl-1*H*-1-indazolecarboxylate

A total of 1.5 g of the title compound was obtained as a colorless powder by subjecting 1.7 g of *tert*-butyl 3-(3-fluorophenyl)-5-(hydroxymethyl)-1*H*-1-indazolecarboxylate produced in Production Example I-24-a to the oxidation procedure of Production Example I-4-b.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.75 (9H, s), 7.22 (1H, dt, J = 2.5, 10.0 Hz), 7.54 (1H, dt, J = 6.1, 8.2 Hz), 7.73 (1H, dd, J = 2.5, 10.0 Hz), 7.80 (1H, d, J = 10.0 Hz), 8.11 (1H, dd, J = 1.5, 8.8 Hz), 8.36 (1H, d, J = 8.8 Hz), 8.48 (1H, s), 10.14 (1H, s).

PRODUCTION EXAMPLE I-25-b

Ethyl (*E*)-3-[3-(3-fluorophenyl)-1*H*-5-indazolyl]-2-propenoate

To a solution of 0.11 ml ethyl diethylphosphonoacetate in 5 ml N,N-dimethylformamide was added 20 mg of sodium hydride (60% oily) under ice-cooling, and the mixture was stirred for 15 minutes. To the reaction mixture was added

a solution of 150 mg of *tert*-butyl 3-(3-fluorophenyl)-5-formyl-1*H*-1-indazolecarboxylate in 1 ml N,N-dimethylformamide, followed by stirring at room temperature for 30 minutes. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:10), to give 0.16 g of *tert*-butyl 5-[(*E*)-3-ethoxy-3-oxo-1-propenyl]-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate as a colorless oil. This product was dissolved in 2 ml of tetrahydrofuran, 0.1 ml of 5 N hydrochloric acid was added and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate for two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 0.14 g of the title compound as a colorless powder.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.25 (3H, t, J = 7.0 Hz), 4.18 (2H, q, J = 7.0 Hz), 6.77 (1H, d, J = 16.1 Hz), 7.24 (1H, dt, J = 2.4, 8.0 Hz), 7.55 (1H, dt, J = 6.4, 8.0 Hz), 7.60 (1H, d, J = 8.8 Hz), 7.79-7.84 (1H, m), 7.84 (1H, d, J = 8.8 Hz), 7.88 (1H, d, J = 16.1 Hz), 7.93 (1H, d, J = 8.0 Hz), 8.48 (1H, s), 13.50-13.60 (1H, bs).

PRODUCTION EXAMPLE I-25-c

(*E*)-3-[3-(3-Fluorophenyl)-1*H*-5-indazolyl]-2-propenoic acid

To a solution of 0.16 g of ethyl (*E*)-3-[3-(3-fluorophenyl)-1*H*-5-indazolyl]-2-propenoate in methanol was added 1 ml of 5 N aqueous sodium hydroxide solution, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was added with diluted hydrochloric acid to be acidic and was extracted with ethyl acetate for two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 90 mg of the title compound as a colorless powder.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.56 (1H, d, J = 16.4 Hz), 7.24 (1H, dt, J = 2.2, 8.2 Hz), 7.55 (1H, dt, J = 6.0, 8.2 Hz), 7.60 (1H, d, J = 8.6 Hz), 7.79-7.83 (1H, m), 7.81 (1H, d, J = 8.8 Hz), 7.83 (1H, d, J = 16.4 Hz), 7.92 (1H, d, J = 8.0 Hz), 8.43 (1H, s), 12.15-12.35 (1H, bs), 13.52 (1H, s).

PRODUCTION EXAMPLE I-26-a

3-Bromo-5-nitro-1*H*-indazole

To a solution of 12.4 g of 5-nitro-1*H*-indazole in 100 ml carbon tetrachloride were added 16.2 g of N-bromosuccinimide and 0.62 g of 2,2'-azobisisobutyronitrile, and the mixture was heated under reflux for 1 hour. The reaction mixture was cooled, and the resulting crystals were filtrated and washed with diethyl ether, to give 24.0 g of the title compound as a pale yellow powder.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.78 (1H, dd, J = 0.5, 9.3 Hz), 8.25 (1H,

dd, J = 2.1, 9.3 Hz), 8.48 (1H, dd, J = 0.5, 2.1 Hz).

PRODUCTION EXAMPLE I-26-b

tert-Butyl 3-bromo-5-nitro-1*H*-1-indazolecarboxylate

To a solution of 24.0 g of 3-bromo-5-nitro-1*H*-indazole and 12.2 g of 4-(dimethylamino)pyridine in 50 ml tetrahydrofuran was added dropwise 23 ml of di-*tert*-butyl dicarbonate at room temperature. After stirring at room temperature for 30 minutes, the mixture was added with water, acidified by adding diluted hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:10), to give 20.5 g of the title compound as colorless needles.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.73 (9H, s), 8.32 (1H, d, J = 9.0 Hz), 8.46 (1H, dd, J = 2.3, 9.0 Hz), 8.59 (1H, d, J = 2.3 Hz).

PRODUCTION EXAMPLE I-26-c

tert-Butyl 3-(3-fluorophenyl)-5-nitro-1*H*-1-indazolecarboxylate

To a solution of 4.5 g of *tert*-butyl 3-bromo-5-nitro-1*H*-1-indazolecarboxylate in 20 ml N,N-dimethylformamide were added 2.8 g of 3-fluorophenylboronic aid, 0.16 g of 2-(di-*tert*-butylphosphino)biphenyl, 60 mg of palladium acetate and 2.31 g of potassium fluoride, and the mixture was heated at 50°C for two days. To the reaction mixture

was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:15), and then recrystallized from diisopropyl ether-hexane, to give 2.2 g of the title compound as a colorless powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.76 (9H, s), 7.22-7.28 (1H, m), 7.56 (1H, dt, J = 5.9, 8.0 Hz), 7.72 (1H, d, J = 9.5 Hz), 7.77 (1H, d, J = 8.0 Hz), 8.38 (1H, d, J = 9.1 Hz), 8.46 (1H, dd, J = 2.0, 9.1 Hz), 8.89 (1H, d, J = 2.0 Hz).

PRODUCTION EXAMPLE I-26-d

tert-Butyl 5-amino-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate

To a solution of 180 mg of *tert*-butyl 3-(3-fluorophenyl)-5-nitro-1*H*-1-indazolecarboxylate in 10 ml tetrahydrofuran was added 100 mg of palladium (5%)-carbon, and the mixture was stirred at room temperature in an atmosphere of hydrogen gas at normal pressure for 3 hours. The reaction mixture was filtrated through Celite and the solvent was evaporated, to give 184 mg of the title compound as a light brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.73 (9H, s), 3.70-3.90 (2H, bs), 6.98 (1H, dd, J = 1.9, 8.7Hz), 7.14 (1H, dt, J = 1.9, 8.1 Hz), 7.16 (1H, d, J = 1.9 Hz), 7.46 (1H, dt, J = 6.0, 8.1 Hz), 7.67 (1H, dt, J = 1.9, 9.7

Hz), 7.74 (1H, d, J = 8.1 Hz), 7.99 (1H, d, J = 8.7 Hz).

PRODUCTION EXAMPLE I-27-a

3-Bromo-6-nitro-1*H*-indazole

To a solution of 5.0 g of 6-nitro-1*H*-indazole in 50 ml dimethylformamide was added 5.73 g of N-bromosuccinimide at room temperature, and the mixture was stirred at the same temperature for 1 hour. After removing the solvent by distillation, the residue was added with 250 ml of ethyl acetate. The mixture was sequentially washed with half-saturated aqueous sodium hydrogencarbonate solution, water and brine, and dried over anhydrous magnesium sulfate. After filtrating the organic layer through a silica gel pat, the solvent was evaporated and the resulting crystals were suspended in toluene, to give 6.59 g of the title compound as light brown crystals.

^{1}H-NMR (400 MHz, DMSO-D6) δ 7.84 (1H, d, J = 8.8 Hz), 8.01 (1H, dd, J = 2.0, 8.8 Hz), 8.50 (1H, d, J = 2.0 Hz).

PRODUCTION EXAMPLE I-27-b

3-(3-Fluorophenyl)-6-nitro-1*H*-indazole

To a solution of 1.0 g of 3-bromo-6-nitro-1*H*-indazole in 10 ml N-methylpyrrolidone were added 2.0 g of (3-fluorophenyl)tri-n-butyltin, and 480 mg of tetrakis(triphenylphosphine)palladium(0), and the mixture was stirred at 180°C for 2 hours. To the reaction mixture was added 60 ml of ethyl acetate. The mixture was sequentially washed with water (x2) and brine, dried over

anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 1:49), to give 302 mg of the title compound as orange crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.30 (1H, td, J = 8.8, 2.8 Hz), 7.61 (1H, td, J = 8.8, 6.4 Hz), 7.79 (1H, dd, J = 8.8, 1.6 Hz), 7.89 (1H, d, J = 7.2 Hz), 8.02 (1H, dd, J = 8.8, 2.0 Hz), 8.36 (1H, d, J = 8.8 Hz), 8.52 (1H, d, J = 2.0 Hz), 14.08 (1H, s).

PRODUCTION EXAMPLE I-27-c

3-(3-Fluorophenyl)-1*H*-6-indazolamine

To a solution of 300 mg of 3-(3-fluorophenyl)-6-nitro-1*H*-indazole in 5 ml methanol and 2.5 ml ethyl acetate was added 60 mg of 20% palladium hydroxide-carbon (water content: 50%), and the mixture was subjected to hydrogenation at room temperature at normal pressure for 7.5 hours. After adding 2.5 ml of ethyl acetate to the reaction mixture, the catalyst was filtered off through Celite. The solvent was evaporated, and the crude product was suspended in ethyl acetate-diisopropyl ether, to give 142 mg of the title compound as white crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 5.72 (2H, s), 6.60 (1H, s), 6.62 (1H, d, J = 8.8 Hz), 7.18 (1H, td, J = 8.4, 2.4 Hz), 7.51 (1H, td, J = 8.0, 6.4 Hz), 7.65 (1H, d, J = 10.8 Hz), 7.73 (1H, d, J = 8.8 Hz), 7.77 (1H, d, J = 7.6 Hz), 12.62 (1H, s).

PRODUCTION EXAMPLE I-28-a

3-(3-Fluorophenyl)-7-nitro-1*H*-indazole

A total of 64 mg of the title compound was obtained as purple crystals by the procedures of Production Examples I-27-a and I-27-b, except from 1.13 g of 7-nitro-1*H*-indazole as a starting material.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.34 (1H, td, J = 8.4, 2.4 Hz), 7.48 (1H, t, J = 8.0 Hz), 7.62 (1H, q, J = 7.6 Hz), 7.79 (1H, dd, J = 10.4, 2.4 Hz), 7.88 (1H, d, J = 7.6 Hz), 8.44 (1H, d, J = 8.0 Hz), 8.64 (1H, d, J = 8.0 Hz), 14.20 (1H, s).

PRODUCTION EXAMPLE I-28-b

3-(3-Fluorophenyl)-1*H*-7-indazolamine

A total of 57 mg of the title compound was obtained as purple crystals by the procedure of Production Example I-27-c, except from 63 mg of 3-(3-fluorophenyl)-7-nitro-1*H*-indazole as a starting material.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 5.43 (2H, s), 6.53 (1H, d, J = 7.2 Hz), 6.96 (1H, dd, J = 7.2, 8.4 Hz), 7.21 (1H, td, J = 8.4, 2.8 Hz), 7.25 (1H, d, J = 8.4 Hz), 7.54 (1H, q, J = 7.6 Hz), 7.69 (1H, d, J = 10.4 Hz), 7.81 (1H, d, J = 8.0 Hz), 12.91 (1H, s).

PRODUCTION EXAMPLE I-29-a

tert-Butyl 3-(2-bromoacetyl)-5-nitro-1*H*-1-indazolecarboxylate

To a solution of 3.0 g of *tert*-butyl 3-bromo-5-nitro-1*H*-1-indazolecarboxylate produced in Production Example I-26-b in 20 ml toluene were added 3.2 ml of tributyl(1-ethoxyvinyl)tin and 620 mg of tetrakis(triphenylphosphine)palladium(0), and the mixture

was heated at 100°C in an atmosphere of nitrogen gas for 6 hours. The reaction mixture was cooled to room temperature, and the solvent was evaporated. To the residue was added 20 ml of tetrahydrofuran, 1.56 g of N-bromosuccinimide was added, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added aqueous sodium thiosulfate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:7), to give 0.9 g of the title compound as colorless needles.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.78 (9H, s), 4.80 (2H, s), 8.34 (1H, dd, J = 0.6, 9.2 Hz), 8.47 (1H, dd, J = 2.3, 9.2 Hz), 9.26 (1H, dd, J = 0.6, 2.3 Hz).

PRODUCTION EXAMPLE I-29-b

tert-Butyl 3-(imidazo[1,2-*a*]pyridin-2-yl)-5-nitro-1*H*-1-indazolecarboxylate

A total of 0.88 g of *tert*-butyl 3-(2-bromoacetyl)-5-nitro-1*H*-1-indazolecarboxylate was dissolved in 10 ml of tetrahydrofuran-methanol (1:1), and 240 mg of 2-aminopyridine and 210 mg of sodium hydrogencarbonate were added, followed by heating under reflux for 1 hour. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The mixture was washed with

water, dried over magnesium sulfate and the solvent was removed. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:7), to give 0.38 g of the title compound as a pale yellow powder.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.69 (9H, s), 7.02 (1H, t, J = 6.6 Hz), 7.37 (1H, t, J = 6.6 Hz), 7.79 (1H, d, J = 7.5 Hz), 8.30 (1H, d, J = 7.5 Hz), 8.50 (1H, dd, J = 2.3, 7.5 Hz), 8.65 (1H, d, J = 6.6 Hz), 8.71 (1H, s), 9.52 (1H, d, J = 2.3 Hz).

PRODUCTION EXAMPLE I-29-c

tert-Butyl 5-amino-3-imidazo[1,2-*a*]pyridin-2-yl-1*H*-1-indazolecarboxylate

A total of 0.48 g of *tert*-butyl 3-imidazo[1,2-*a*]pyridin-2-yl-5-nitro-1*H*-1-indazolecarboxylate was subjected to treatment by the procedure of Production Example I-26-d, and purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:7), to give 0.11 g of the title compound as a light brown powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.74 (9H, s), 6.84 (1H, t, J = 6.7 Hz), 6.98 (1H, dd, J = 2.4, 8.9 Hz), 7.22 (1H, dd, J = 6.7, 8.9 Hz), 7.71 (1H, d, J = 8.9 Hz), 7.93 (1H, d, J = 8.9 Hz), 7.95 (1H, d, J = 2.4 Hz), 8.19 (1H, d, J = 6.7 Hz), 8.33 (1H, s).

PRODUCTION EXAMPLE I-30-a

tert-Butyl 5-(azidomethyl)-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate

To a solution of 600 mg of *tert*-butyl 5-(chloromethyl)-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate

produced in Production Example I-24-b in 4 ml dimethyl sulfoxide was added 162 mg of sodium azide, and the mixture was stirred at room temperature for 50 minutes. To the reaction mixture was added 25 ml of diethyl ether. The mixture was sequentially washed with water (x3) and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 571 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 1.69 (9H, s), 4.66 (2H, s), 7.42 (1H, td, J = 8.0, 2.8 Hz), 7.67 (1H, td, J = 8.0, 6.0 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.77 (1H, d, J = 10.0 Hz), 7.87 (1H, d, J = 8.0 Hz), 8.19 (1H, d, J = 8.0 Hz), 8.21 (1H, s).

PRODUCTION EXAMPLE I-30-b

tert-Butyl 5-(aminomethyl)-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate

To a solution of 550 mg of *tert*-butyl 5-(azidomethyl)-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate in a mixture of 10 ml ethanol and 5 ml tetrahydrofuran was added 110 mg of 5% palladium-calcium carbonate, and the mixture was hydrogenated at room temperature at normal pressure for 1.5 hours. After filtering off the catalyst through Celite, the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:methanol = 1:0 to 9:1), to give 427 mg of the title compound as light green crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 1.68 (9H, s), 1.99 (2H, s), 3.89 (2H, s),

7.40 (1H, td, J = 8.8, 2.8 Hz), 7.64 (1H, d, J = 8.4 Hz), 7.65 (1H, td, J = 8.0, 6.4 Hz), 7.78 (1H, d, J = 10.0 Hz), 7.87 (1H, d, J = 8.4 Hz), 8.07 (1H, s), 8.09 (1H, d, J = 8.8 Hz).

PRODUCTION EXAMPLE I-30-c

[3-(3-Fluorophenyl)-1*H*-5-indazolyl]methanamine

To a solution of 300 mg of *tert*-butyl 5-(aminomethyl)-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate in 1 ml methylene chloride was added 2 ml of trifluoroacetic acid, and the mixture was stirred at room temperature for 6.5 hours. After removing the solvent by filtration, to the residue was added 20 ml of ethyl acetate. The mixture was sequentially washed with saturated aqueous sodium hydrogencarbonate solution (x2) and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 188 mg of the title compound as yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.90 (2H, s), 7.24 (1H, td, J = 8.4, 2.4 Hz), 7.40 (1H, d, J = 8.4 Hz), 7.55 (1H, d, J = 8.4 Hz), 7.57 (1H, td, J = 8.0, 6.4 Hz), 7.76 (1H, d, J = 10.4 Hz), 7.87 (1H, d, J = 8.0 Hz), 8.05 (1H, s), 13.30 (1H, s).

PRODUCTION EXAMPLE I-31

tert-Butyl 3-(3-fluorophenyl)-5-(iodomethyl)-1*H*-1-indazolecarboxylate

To a solution of 500 mg of *tert*-butyl 5-(chloromethyl)-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate produced in Production Example I-24-b in 2.5 ml acetone was added 218 mg of sodium iodide, and the mixture was stirred

at room temperature for 2 hours. After filtering off the resulting sodium chloride through Celite, the solvent was evaporated, to give 638 mg of the title compound as bright yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 1.68 (9H, s), 4.87 (2H, s), 7.42 (1H, td, J = 8.4, 2.8 Hz), 7.67 (1H, td, J = 8.0, 6.4 Hz), 7.70-7.78 (2H, m), 7.87 (1H, d, J = 8.4Hz), 8.11 (1H, d, J = 8.8 Hz), 8.28 (1H, s).

PRODUCTION EXAMPLE I-32-a

Methyl 3-(3-fluorophenyl)-1-trityl-1*H*-5-indazolecarboxylate

To a solution of 2.43 g of methyl 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylate produced in Production Example I-4-e in 25 ml tetrahydrofuran was added 720 mg of 60% sodium hydride (oily), and the mixture was stirred under ice-cooling for 10 minutes. Then, 3.26 g of chlorotriphenylmethane was added and the mixture was stirred at the same temperature for 30 minutes and at room temperature for 1 hour. The reaction mixture was ice-cooled, saturated aqueous sodium hydrogencarbonate solution was added, and the mixture was extracted with 100 ml of ethyl acetate. The organic layer was sequentially washed with water and brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was crystallized from ethyl acetate-diisopropyl ether, to give 3.48 g of the title compound as white crystals. In addition, the mother liquor was concentrated, and then the residue was crystallized from diisopropyl ether, to give

0.37 g of the title compound as white crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.85 (3H, s), 6.58 (1H, d, J = 8.8 Hz), 7.22 (6H, d, J = 6.8 Hz), 7.28-7.40 (10H, m), 7.58-7.64 (2H, m), 7.68 (1H, dd, J = 9.2, 1.2 Hz), 7.74 (1H, d, J = 7.6 Hz), 8.62 (1H, s).

PRODUCTION EXAMPLE I-32-b

[3-(3-Fluorophenyl)-1-trityl-1*H*-5-indazolyl]methanol

Under ice-cooling, a solution of 3.85 g of methyl 3-(3-fluorophenyl)-1-trityl-1*H*-5-indazolecarboxylate in 40 ml tetrahydrofuran was added 535 mg of lithium aluminium hydride, and the mixture was stirred at the same temperature for 5 minutes and at room temperature for further 30 minutes. The reaction mixture was ice-cooled, saturated aqueous sodium sulfate solution was added, aluminium hydroxide was precipitated, and the organic layer was decanted. To the residue was added 20 ml of tetrahydrofuran, stirred, and the organic layer was re-decanted twice. The solvent was evaporated from the collected organic layers. The residue was dissolved in 80 ml of ethyl acetate, and then the mixture was sequentially washed with water and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The resulting crude crystals were recrystallized from diisopropyl ether, to give 3.37 g of the title compound as white needles.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 4.55 (2H, d, J = 6.0 Hz), 5.18 (1H, t, J = 6.0 Hz), 6.43 (1H, d, J = 8.8 Hz), 7.07 (1H, d, J = 8.8 Hz), 7.21 (6H, d, J = 6.8 Hz), 7.27-7.40 (10H, m), 7.52-7.62 (2H, m), 7.74 (1H, d, J

= 7.6 Hz), 8.01 (1H, s).

PRODUCTION EXAMPLE I-32-c

5-(Chloromethyl)-3-(3-fluorophenyl)-1-trityl-1*H*-indazole

Under ice-cooling, a solution of 1.21 g of [3-(3-fluorophenyl)-1-trityl-1*H*-5-indazolyl]methanol in 12 ml methylene chloride were added 0.45 ml of triethylamine and 0.23 ml of methanesulfonyl chloride, and the mixture was stirred at room temperature overnight. To the reaction mixture was added 150 ml of ethyl acetate. The mixture was sequentially washed with water, saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The resulting crude crystals were recrystallized from diisopropyl ether, to give 1.13 g of the title compound as white crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 4.87 (2H, s), 6.49 (1H, d, J = 8.8 Hz), 7.18 (1H, d, J = 8.8 Hz), 7.21 (6H, d, J = 6.8 Hz), 7.25-7.40 (10H, m), 7.56 (1H, td, J = 8.0, 7.2Hz), 7.62 (1H, d, J = 10.0 Hz), 7.75 (1H, d, J = 7.6 Hz), 8.24 (1H, s).

PRODUCTION EXAMPLE I-33

tert-Butyl 5-(hydroxymethyl)-3-(2-naphthyl)-1*H*-1-indazolecarboxylate

A total of 3.7 g of the title compound was obtained as colorless crystals by the procedure of Production Example I-24-a, except from, as a starting material, 4.1 g of methyl 3-(2-naphthyl)-1*H*-5-indazolecarboxylate produced in

Production Example I-12-a.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.69 (9H, s), 4.69 (2H, d, J = 5.5 Hz), 5.37 (1H, t, J = 5.5 Hz), 7.61 (1H, d, J = 9.6 Hz), 7.61 (1H, ddd, J = 1.3, 3.2, 9.6 Hz), 7.64 (1H, dd, J = 1.6, 8.5 Hz), 7.99-8.03 (1H, m), 8.08-8.12(1H, m), 8.11 (1H, d, J = 1.6 Hz), 8.14 (1H, d, J = 8.5 Hz), 8.14-8.17 (1H, m), 8.17-8.19 (1H, m), 8.58 (1H, bs).

PRODUCTION EXAMPLE I-34

[3-(3-Fluorophenyl)-1-(methoxymethyl)-1*H*-5-indazolyl]methanol

A total of 1.0 g of methyl 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylate obtained in Production Example I-4-e was dissolved in 15 ml of N,N-dimethylformamide, and 200 mg of sodium hydride (60% oily) was added under ice-cooling, followed by stirring for 30 minutes. To the reaction mixture was added 0.4 ml of chloromethyl methyl ether, followed by stirring at room temperature for 30 minutes. To the reaction mixture was added water and the mixture was extracted with ethyl acetate for two times. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:10), to give 0.95 g of methyl 3-(3-fluorophenyl)-1-(methoxymethyl)-1H-5-indazolecarboxylate as colorless needles. This compound was dissolved in 15 ml of tetrahydrofuran, and 8.0 ml of a solution of diisobutylaluminium hydride in toluene was added dropwise

at room temperature. While cooling the reaction mixture, water was added. The mixture was acidified with diluted hydrochloric, and extracted with ethyl acetate for two times. The organic layer was washed with sodium hydrogencarbonate and water, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 0.78 g of the title compound as a colorless oil.

^{1}H-NMR(400MHz, $CDCl_3$) δ 3.36 (3H, s), 4.85 (2H, d, J = 5.0 Hz), 5.76 (2H, s), 7.11 (1H, dt, J = 2.8, 8.3 Hz), 7.48 (1H, dt, J = 6.5, 8.3 Hz), 7.50 (1H, d, J = 8.9 Hz), 7.62 (1H, d, J = 8.9 Hz), 7.68 (1H, d, J = 10.9 Hz), 7.77 (1H, d, J = 8.9 Hz), 8.00 (1H, s).

PRODUCTION EXAMPLE I-35-a

3-Bromo-1*H*-indazole

A total of 1.58 g of the title compound was obtained as beige crystals by the procedure of Production Example I-14-a, except from 1.00 g of 1*H*-indazole.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.23 (1H, tt, J = 8.0, 1.2 Hz), 7.46 (1H, tt, J = 8.0, 1.2 Hz), 7.58 (1H, dd, J = 8.0, 1.2 Hz).

PRODUCTION EXAMPLE I-35-b

3-(3-Fluorophenyl)-1*H*-indazole

A total of 42 mg of the title compound was obtained as white crystals by the procedure of Production Example I-27-b, except from 200 mg of 3-bromo-1*H*-indazole.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.20-7.28 (2H, m), 7.43 (1H, td, J = 8.0, 1.2 Hz) 7.57 (1H, td, J = 8.0, 6.0 Hz), 7.61 (1H, dd, J = 8.0, 0.8 Hz), 7.75 (1H, ddd, J = 10.4, 2.8, 1.2 Hz), 7.86 (1H, ddd, J = 8.0, 1.2,

1.2 Hz), 8.10(1H, dd, J = 8.0, 0.8 Hz), 13.37 (1H, s).

PRODUCTION EXAMPLE I-36-a

1-(2,2-Diethoxyethoxy)-4-fluorobenzene

To a solution of 10.0 g of 4-fluorophenol and 16.1 ml of bromoacetaldehyde diethylacetal in 100 ml dimethylformaldehyde was added 18.5 g of potassium carbonate at room temperature, and the mixture was stirred at 120°C for two days. The reaction mixture was filtered through Celite, and the filtrate was diluted with ethyl acetate. The organic layer was sequentially washed with saturated aqueous ammonium chloride solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:n-hexane = 0:10 to 1:20), to give 17.3 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t, J = 7.2 Hz), 3.58-3.67 (2H, m), 3.71-3.80 (2H, m), 3.97 (2H, d, J = 5.2 Hz), 4.82 (1H, t, J = 5.2 Hz), 6.84-6.88 (2H, m), 6.93 - 6.99 (2H, m).

PRODUCTION EXAMPLE I-36-b

5-Fluoro[*b*]benzofuran

To a solution of 16.0 g of 1-(2,2-diethoxyethoxy)-4-fluorobenzene in 50 ml n-hexane was added 3.2 g of amberlyst 15 at room temperature. After the mixture was treated in a sealed tube at 200°C for 11 hours, the amberlyst 15 was filtered off. The solvent was evaporated,

and the crude product was purified and separated by silica gel column chromatography (n-hexane), to give 4.8 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.74 (1H, dd, J = 1.2, 2.4 Hz), 7.02 (1H, dt, J = 2.4, 8.8 Hz), 7.25 (1H, dd, J = 2.4, 8.8 Hz), 7.41 - 7.44 (1H, m), 7.65 (1H, d, J = 2.4 Hz).

PRODUCTION EXAMPLE I-36-c

5-Fluoro-2-benzo[*b*]furanboronic acid

In a nitrogen atmosphere, to a solution of 2.0 g of 5-fluorobenzofuran in 150 ml tetrahydrofuran was added 18.5 ml of a 1.59 M solution of n-butyllithium in n-hexane at -78°C, and the mixture was stirred at the same temperature for 10 minutes and at 0°C for further 10 minutes. At -78°C, 3.7 ml of triethoxyborane was added, and the mixture was stirred for 2 hours while elevating to 0°C. 30 ml of 1 N hydrochloric acid was added, stirred at room temperature for 1 hour, and then the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:n-hexane = 1:3 to 1:1), to give 525 mg of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, dt, J = 2.4, 8.8 Hz), 7.29 (1H, dd, J = 2.4, 8.8 Hz), 7.33 (1H, s), 7.44 (1H, dd, J = 4.0, 8.8 Hz).

PRODUCTION EXAMPLE I-36-d

3-Iodo-5-nitro-1*H*-indazole

To a solution of 17.0 g of 5-nitroindazole in 100 ml dimethylformamide was added 24.6 g of N-iodosuccinimide at room temperature, and the mixture was stirred at 80°C for 7 hours. After standing to cool, to the reaction mixture were added 150 ml of water and 200 ml of diethyl ether, and the resulting crystals were collected by filtration. The crystals were sequentially washed with water, isopropanol and diethyl ether, to give 27.5 g of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.74 (1H, d, J = 9.2 Hz), 8.23 (1H, dd, J = 2.4, 9.2 Hz), 8.30 (1H, d, J = 2.4 Hz), 12.01 (1H, brs).

PRODUCTION EXAMPLE I-36-e

3-Iodo-5-nitro-1-trityl-1*H*-indazole

To a solution of 27.5 g of 3-iodo-5-nitro-1*H*-indazole in 300 ml tetrahydrofuran at 0°C in an atmosphere of nitrogen gas was added 6.1 g of 60% sodium hydride, and the mixture was stirred at the same temperature for 10 minutes. To the mixture was added 39.8 g of trityl chloride, followed by stirring at room temperature for 1 hour. Water was added and the mixture was diluted with ethyl acetate. The organic layer was sequentially washed with saturated aqueous ammonium chloride solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The resulting crude crystals were washed with diethyl ether, to give 48.5 g of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 6.42 (1H, d, J = 9.2 Hz), 7.13-7.32 (15H,

m), 7.89 (1H, ddd, J = 0.4, 2.4, 9.2 Hz), 8.44 (1H, d, J = 2.4 Hz).

PRODUCTION EXAMPLE I-36-f

3-(5-Fluoro[*b*]benzofuran-2-yl)-5-nitro-1-trityl-1*H*-indazole

A total of 255 mg of the title compound was obtained as pale yellow crystals by the procedure of Production Example I-26-c, except from 500 mg of 3-iodo-5-nitro-1-trityl-1*H*-indazole and 178 mg of 5-fluoro-2-benzo[*b*]furanboronic acid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.49 (1H, dd, J = 0.8, 9.2 Hz), 7.08 (1H, dt, J = 2.4, 9.2 Hz), 7.15-7.36 (17H, m), 7.59 (1H, dd, J = 4.0, 9.2 Hz), 7.90 (1H, dd, J = 2.4, 9.2 Hz), 9.25 (1H, dd, J = 0.8, 2.4 Hz).

PRODUCTION EXAMPLE I-36-g

3-(5-Fluoro[*b*]benzofuran-2-yl)-1-trityl-1*H*-indazol-5-ylamine

A total of 178 mg of the title compound was obtained as colorless crystals by the procedure of Production Example I-26-d, except from 250 mg of 3-(5-fluorobenzo[*b*]furan-2-yl)-5-nitro-1-trityl-1*H*-indazole as a starting material.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.67 (2H, brs), 6.25 (1H, dd, J = 0.8, 9.2 Hz), 6.49 (1H, dd, J = 2.4, 9.2 Hz), 6.97 (1H, dt, J = 2.4, 9.2 Hz), 7.02 (1H, d, J = 0.8 Hz), 7.20 (1H, dd, J = 2.4, 9.2 Hz), 7.20-7.31 (15H, m), 7.45 (1H, d, J = 2.4 Hz), 7.47 (1H, dd, J = 4.0, 9.2 Hz).

EXAMPLE I-1

*N*5-(3-Pyridylmethyl)-3-(4-fluorophenyl)-1*H*-5-indazolecarboxamide

To a solution of 150 mg of 3-(4-fluorophenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-14 in 2.5 ml dimethylformamide were added a solution of 70 mg of 3-picolylamine in 0.5 ml dimethylformamide and 124 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (= WSC.HCl), and the mixture was stirred at room temperature for four days. After removing the solvent by distillation, the residue was dissolved in 25 ml of ethyl acetate. The mixture was sequentially washed with water and brine, dried over anhydrous magnesium sulfate and the solvent was removed. The resulting crude crystals were recrystallized from ethyl acetate-diisopropyl ether, to give 109 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D6) δ 4.55 (1H, d, J = 5.6 Hz), 7.34-7.44 (3H, m), 7.65 (1H, d, J = 8.8 Hz), 7.75 (1H, d, J = 7.2 Hz), 7.96 (1H, d, J = 8.8 Hz), 8.07 (2H, dd, J = 5.6, 8.8 Hz), 8.46 (1H, d, J = 8.0 Hz), 8.58 (1H, s), 8.61 (1H, s), 9.23 (1H, t, J = 5.6 Hz), 13.49 (1H, s).

EXAMPLE I-2

*N*5-(3-Pyridylmethyl)-3-(3-chlorophenyl)-1*H*-5-indazolecarboxamide

A total of 36 mg of the title compound was obtained as white needles by the procedure of Example I-1, except from 60 mg of 3-(3-chlorophenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-15 and 35 mg of 3-picolylamine.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 4.56 (1H, d, J = 5.6 Hz), 7.36 (1H, dd, J

= 4.8, 8.0 Hz), 7.51 (1H, d, J = 8.0 Hz), 7.61 (1H, t, J = 8.0 Hz), 7.66 (1H, d, J = 8.8 Hz), 7.76 (1H, d, J = 8.0 Hz), 7.97 (1H, d, J = 8.0 Hz), 8.02 (1H, s), 8.03 (1H, d, J = 8.8 Hz), 8.46 (1H, dd, J = 1.6, 4.8 Hz), 8.59 (1H, d J = 1.6 Hz), 8.62 (1H, s), 9.26 (1H, t, J = 5.6 Hz), 13.62 (1H, s).

EXAMPLE I-3

*N*5-(3-Pyridylmethyl)-3-[3-(trifluoromethyl)phenyl]-1*H*-5-indazolecarboxamide

A total of 28 mg of the title compound was obtained as white crystals by the procedure of Example I-1, except from 53 mg of 3-[3-(trifluoromethyl)phenyl]-1*H*-5-indazolecarboxylic acid produced in Production Example I-16 and 28 mg of 3-picolylamine.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 4.56 (2H, d, J = 6.0 Hz), 7.37 (1H, dd, J = 4.8, 8.0 Hz), 7.69 (1H, d, J = 8.8 Hz), 7.76 (1H, d, J = 8.0 Hz), 7.79-7.87 (2H, m), 7.98 (1H, d, J = 8.8 Hz), 8.28 (1H, s), 8.38 (1H, d, J = 6.0 Hz), 8.46 (1H, d, J = 4.8 Hz), 8.59 (1H, s), 8.64 (1H, s), 9.26 (1H, t, J = 6.0 Hz), 13.69 (1H, s).

EXAMPLE I-4

*N*5-(3-Pyridylmethyl)-3-(3-methoxyphenyl)-1*H*-5-indazolecarboxamide

A total of 8 mg of the title compound was obtained as a white amorphous powder by the procedure of Example I-1, except from 14 mg of 3-(3-methoxyphenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-18 and 12 mg of 3-picolylamine.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 4.56 (2H, d, J = 5.6 Hz), 7.02 (1H, d, J = 8.0 Hz), 7.37 (1H, dd, J = 4.8, 7.6 Hz), 7.48 (1H,,t, J = 8.0 Hz), 7.53 (1H, s), 7.62 (1H, d, J = 8.4 Hz), 7.64 (1H, d, J = 8.0Hz), 7.75 (1H, d, J = 7.6 Hz), 7.95 (1H, d, J = 8.4 Hz), 8.46 (1H, d, J = 4.8 Hz), 8.58 (1H, s), 8.62 (1H, s), 9.26 (1H, t, J = 5.6 Hz), 13.49 (1H, s).

EXAMPLE I-5

*N*5-[(1*S*)-1-(Hydroxymethyl)-2-methylpropyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

A total of 50 mg of the title compound was obtained as a colorless powder by the procedure of Example I-1, except from 150 mg of 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-4 and 1.2 ml of 0.5 M solution of valinol in acetonitrile as starting materials.

^{1}H-NMR(400MHz,DMSO-d_6) δ 0.90 (3H, d, J = 8.0 Hz), 0.92 (3H, d, J = 8.0 Hz), 1.88-2.00 (1H, m), 3.48-3.60 (2H, m), 3.78-3.87 (1H, m), 4.55-4.66 (1H, m), 7.23-7.30 (1H, m), 7.56-7.65 (1H, m), 7.62 (1H, d, J = 8.4 Hz), 7.80 (1H, d, J = 10.1 Hz), 7.86-7.96 (2H, m), 8.15 (1H, d, J = 8.4 Hz), 8.54 (1H, s)

EXAMPLE I-6

*N*5-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

A total of 20 mg of the title compound was obtained as a colorless powder by the procedure of Example I-1, except from 50 mg of 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-4 and 30 mg of R(-)-2-phenylglycinol as starting materials.

^{1}H-NMR(400MHz, DMSO-d_6) δ 3.64-3.79 (2H, m), 4.88 (1H, t, J = 6.0 Hz), 5.12 (1H, dt, J = 5.7, 8.2 Hz), 7.19-7.24 (1H, m), 7.28 (1H, dt, J = 2.4, 8.2 Hz), 7.29-7.34 (2H, m), 7.38-7.42 (2H, m), 7.61 (1H, dt, J = 6.3, 8.2 Hz), 7.64 (1H, d, J = 8.9 Hz), 7.80 (1H, d, J = 10.1 Hz), 7.90 (1H, d, J = 7.7 Hz), 7.95 (1H, d, J = 8.9 Hz), 8.61 (1H, s), 8.84 (1H, d, J = 8.2 Hz), 13.57 (1H, s)

EXAMPLE I-7

*N*5-[(1*S*)-2-Hydroxy-1-phenethyl]-3-benzo[*b*]thiophen-3-yl-1*H*-5-indazolecarboxamide

To a solution of 50 mg of 3-benzo[*b*]thiophen-3-yl-1*H*-5-indazolecarboxylic acid produced in Production Example I-19 in 4 ml dimethylformamide were added 28 mg of (2*S*)-2-amino-2-phenyl-1-ethanol, 39 mg of 1-hydroxybenzotriazole monohydrate, and 49 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and the mixture was stirred at room temperature for five days. To the reaction mixture was added 40 ml of ethyl acetate, and the mixture was sequentially washed with water, 1 N hydrochloric acid, water, saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was removed. The resulting crude crystals were recrystallized from ethyl acetate-diethyl ether, to give 46 mg of the title compound as pale red crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.66-3.81 (2H, m) 5.00 (1H, t, J = 5.6 Hz), 5.16 (1H, td, J = 8.0, 5.6 Hz), 7.24 (1H, t, J = 7.6 Hz), 7.33 (2H, t,

J = 7.6 Hz), 7.42 (2H, d, J = 7.6 Hz), 7.45-7.55 (2H, m), 7.68 (1H, d, J = 8.8 Hz), 7.99 (1H, d, J = 8.4 Hz), 8.11 (1H, d, J = 8.8Hz), 8.50 (1H, s), 8.65-8.70 (2H, m), 8.81 (1H, d, J = 8.0 Hz), 13.55 (1H, s).

EXAMPLE I-8

N5-[1-(Hydroxymethyl)cyclopentyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

A total of 16 mg of the title compound was obtained as a colorless powder by the procedure of Example I-7, except from 180 mg of 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-4 and 115 mg of 1-amino-1-cyclopentanemethanol as starting materials.

^{1}H-NMR(400MHz, DMSO-d_6) δ 1.51-1.60 (2H, m), 1.63-1.72 (2H, m), 1.72-1.80 (2H, m), 1.97-2.07 (2H, m), 3.60 (2H, d, J = 6.1 Hz), 4.87 (1H, t, J = 6.1 Hz), 7.26 (1H, dt, J = 2.7, 8.7 Hz), 7.59 (1H, dt, J = 6.3, 7.9 Hz), 7.59 (1H, d, J = 8.6 Hz), 7.80 (1H, ddd, J = 1.6, 2.7, 10.5 Hz), 7.94 (1H, s), 8.49 (1H, s), 13.51 (1H, s)

EXAMPLE I-9

N5-(2-Hydroxy-2-phenylethyl)-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

A total of 75 mg of the title compound was obtained as a colorless powder by the procedure of Example I-7, except from 180 mg of 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-4 and 137 mg of 2-amino-1-phenylethanol as starting materials.

^{1}H-NMR(400MHz, DMSO-d_6) δ 3.30-3.37 (1H, m), 3.51 (1H, ddd, J = 4.6, 5.8, 13.2 Hz), 4.80 (1H, dd, J = 4.6, 8.3 Hz), 5.56 (1H, d, J = 4.6 Hz),

7.21-7.26 (1H, m), 7.28 (1H, dt, J = 2.4, 8.4 Hz), 7.30-7.35 (2H, m), 7.36-7.40 (2H, m), 7.60 (1H, dt, J = 6.3, 8.4 Hz), 7.62 (1H, d, J = 9.2 Hz), 7.81 (1H, d, J = 10.4 Hz), 7.90 (1H, d, J = 9.2 Hz), 7.90 (1H, d, J = 8.4 Hz), 8.54 (1H, s), 8.76 (1H, d, J = 5.8 Hz), 13.54 (1H, bs)

EXAMPLE I-10

*N*5-(2-Hydroxypropyl)-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

A total of 60 mg of the title compound was obtained as a colorless oily substance by the procedure of Example I-7, except from 180 mg of 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-4 and 0.08 ml of 1-amino-2-propanol as starting materials.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.29 (3H, d, J = 5.0Hz), 3.38 (1H, ddd, J = 4.9, 7.4, 14.0 Hz), 3.73 (1H, ddd, J = 3.0, 6.5, 14.0 Hz), 4.06-4.13 (1H, m), 6.75-6.81 (1H, m), 7.14 (1H, dt, J = 2.5, 8.1 Hz), 7.49 (1H, dt, J = 6.2, 8.1 Hz), 7.55 (1H, d, J = 8.8 Hz), 7.68 (1H, ddd, J = 1.4, 2.5, 9.7 Hz), 7.76 (1H, d, J = 8.1 Hz), 7.86 (1H, dd, J = 1.8, 8.8 Hz), 8.49 (1H, d, J = 1.8 Hz)

EXAMPLE I-11

*N*5-[1-(4-Chlorophenyl)-2-hydroxyethyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

A total of 55 mg of the title compound was obtained as a colorless powder by the procedure of Example I-7, except from 180 mg of 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-4 and 112 mg of 2-amino-2-(4-chlorophenyl)-1-ethanol as starting materials.

^{1}H-NMR(400MHz, $CDCl_3$) δ 4.03 (1H, dd, J = 5.4, 11.4 Hz), 4.07 (1H, dd, J = 4.1, 11.4 Hz), 5.30 (1H, ddd, J = 4.1, 5.4, 11.4 Hz), 7.02 (1H, d, J = 7.0 Hz), 7.14 (1H, dt, J = 2.3, 8.0 Hz), 7.36 (4H, s), 7.49 (1H, dt, J = 6.0, 8.0 Hz), 7.56 (1H, d, J = 8.7 Hz), 7.68 (1H, ddd, J = 1.5, 2.3, 9.9 Hz), 7.76 (1H, d, J = 8.0 Hz), 7.87 (1H, dd, J = 1.7, 8.7 Hz), 8.55 (1H, d, J = 1.7 Hz)

EXAMPLE I-12

*N*5-{2-Hydroxy-1-[4-(trifluoromethyl)phenyl]ethyl}-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

A total of 80 mg of the title compound was obtained as a colorless powder by the procedure of Example I-7, except from 162 mg of 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-4 and 130 mg of 2-amino-2-[4-(trifluoromethyl)phenyl]-1-ethanol as starting materials.

^{1}H-NMR(400MHz, DMSO-d_6) δ 3.66-3.83 (2H, m), 5.07 (1H, t, J = 5.5 Hz), 5.12-5.22 (1H, m), 7.28 (1H, dt, J = 2.5, 8.7 Hz), 7.58-7.68 (2H, m), 7.65 (2H, d, J = 8.2 Hz), 7.69 (2H, d, J = 8.2 Hz), 7.80 (1H, bd, J = 10.5 Hz), 7.90 (1H, d, J = 8.7 Hz), 7.94 (1H, d, J = 8.8 Hz), 8.62 (1H, s), 8.94 (1H, d, J = 7.8 Hz), 13.58 (1H, s)

EXAMPLE I-13

*N*5-(2,3-Dihydroxypropyl)-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

A total of 40 mg of the title compound was obtained as a colorless oily substance by the procedure of Example I-7, except from 180 mg of 3-(3-fluorophenyl)-1*H*-5-

indazolecarboxylic acid produced in Production Example I-4 and 0.08 ml of 3-amino-1,2-propanediol as starting materials.

^{1}H-NMR(400MHz, $CDCl_3$) δ 3.17-3.24 (1H, m), 3.24-3.40 (2H, m), 3.40-3.57 (1H, m), 3.62-3.70 (1H, m), 4.59 (1H, bs), 4.86 (1H, bs), 7.27 (1H, dt, J = 2.2, 8.4 Hz), 7.60 (1H, dt, J = 6.3, 8.4 Hz), 7.63 (1H, d, J = 9.0 Hz), 7.81 (1H, d, J = 10.1 Hz), 7.91 (1H, d, J = 8.4 Hz), 7.93 (1H, d, J = 9.0 Hz), 8.59 (1H, s), 8.65 (1H, t, J = 5.6 Hz)

EXAMPLE I-14

*N*5-[1-(2-Fluorophenyl)-2-hydroxyethyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

A total of 51 mg of the title compound was obtained as a colorless powder by the procedure of Example I-7, except from 180 mg of 3-(3-fluorophenyl)-1*H*-5-indazolecarboxylic acid produced in Production Example I-4 and 155 mg of 2-(2-fluorophenyl)glycinol as starting materials.

^{1}H-NMR(400MHz, $CDCl_3$) δ 3.66 (1H, dd, J = 5.3, 11.0 Hz), 3.72 (1H, dd, J = 8.0, 11.0 Hz), 5.10 (1H, t, J = 6.0 Hz), 5.41 (1H, ddd, J = 5.3, 8.0, 8.1 Hz), 7.13-7.19 (2H, m), 7.25-7.31 (2H, m), 7.50 (1H, dt, J = 2.4, 7.9 Hz), 7.62 (1H, dt, J = 6.3, 7.9 Hz), 7.64 (1H, d, J = 8.9 Hz), 7.80 (1H, ddd, J = 1.6, 2.4, 10.5 Hz), 7.90 (1H, d, J = 7.9 Hz), 7.94 (1H, dd, J = 1.6, 9.0 Hz), 8.62 (1H, s), 8.90 (1H, d, J = 8.1 Hz)

EXAMPLE I-15

*N*3-[3-(3-Fluorophenyl)-1*H*-5-indazolyl]nicotinamide

To a solution of 100 mg of *tert*-butyl 5-amino-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate produced in

Production Example I-26 and 0.1 ml of triethylamine in 5 ml tetrahydrofuran was added 55 mg of nicotinic acid chloride hydrochloride, and the mixture was stirred at room temperature for two days. After the completion of the reaction, the reaction mixture was treated with 5 N hydrochloric acid by the procedure of Production Example I-25-b, to give 62 mg of the title compound as a colorless powder.

^{1}H-NMR(400MHz, DMSO-d_6) δ 7.24 (1H, dt, J = 2.4, 8.3 Hz), 7.55-7.63 (3H, m), 7.69 (1H, ddd, J = 1.7, 2.4, 10.2 Hz), 7.79 (1H, s), 7.80 (1H, d, J = 8.3 Hz), 8.32 (1H, dt, J = 1.9, 8.1 Hz), 8.57 (1H, s), 8.76 (1H, dd, J = 1.9, 5.0 Hz), 9.14 (1H, d, J = 2.4 Hz) 10.53 (1H, s), 13.39 (1H, s)

EXAMPLE I-16

N1-[3-(3-Fluorophenyl)-1*H*-5-indazolyl]-2-(2-thienyl)acetamide

A total of 20 mg of the title compound was obtained as a colorless powder by the procedure of Example I-15, except from 120 mg of *tert*-butyl 5-amino-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate produced in Production Example I-26 and 0.05 ml of 2-thiopheneacetic acid chloride as starting materials.

^{1}H-NMR(400MHz, DMSO-d_6) δ 4.01 (2H, s), 7.06-7.13 (3H, m), 7.34 (1H, dd, J = 1.8, 4.6 Hz), 7.38 (1H, dd, J = 1.6, 8.6 Hz), 7.41 (1H, bs), 7.45 (1H, d, J = 8.6 Hz), 7.47 (1H, dt, J = 6.0, 7.8 Hz), 7.64 (1H, d, J = 9.9 Hz), 7.72 (1H, d, J = 7.8 Hz), 8.20 (1H, d, J = 1.6 Hz)

EXAMPLE I-17

*N*1-[3-(3-Fluorophenyl)-1*H*-5-indazolyl]-2-(4-pyridyl)acetamide

A solution of 50 mg of *tert*-butyl 5-amino-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate produced in Production Example I-26, 26 mg of 4-pyridylacetic acid hydrochloride and 0.05 ml of triethylamine in 5 ml tetrahydrofuran was added 37 mg of 1,1'-carbonyldiimidazole as a condensing agent at room temperature. After the completion of the reaction, the reaction mixture was treated with 5 N hydrochloric acid by the procedure of Production Example I-25-b, to give 11 mg of the title compound as a colorless powder.

^{1}H-NMR(400MHz, DMSO-d_6) δ 3.73 (2H, s), 7.15 (1H, dd, J = 1.8, 9.1 Hz), 7.20-7.27 (1H, m), 7.30 (2H, d, J = 8.8 Hz), 7.48 (2H, d, J = 8.8 Hz), 7.55-7.60 (5H, m), 10.03 (1H, bs), 13.35 (1H, s)

EXAMPLE I-18

N-[3-(3-Fluorophenyl)-1*H*-5-indazolyl]methanesulfonamide

A solution of 50 mg of *tert*-butyl 5-amino-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate produced in Production Example I-26 in 2 ml tetrahydrofuran were added 30 μl of triethylamine and 15 μl of methanesulfonyl chloride, and the mixture was stirred at room temperature for 10 hours. The reaction mixture was diluted with water and was extracted with ethyl acetate. The organic layer was sequentially washed with 1 N hydrochloric acid, water,

saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was removed. The resulting crude crystals were recrystallized from ethyl acetate-diethyl ether, to give 26 mg of the title compound as a colorless powder.

^{1}H-NMR(400MHz, DMSO-d_6) δ 2.92 (3H, s), 7.24 (1H, dt, J = 2.7, 8.8 Hz), 7.33 (1H, dd, J = 1.8, 8.8 Hz), 7.57 (1H, t, J = 7.5 Hz), 7.59 (1H, d, J = 8.8 Hz), 7.65 (1H, d, J = 10.4 Hz), 7.78 (1H, d, J = 7.5 Hz), 7.86 (1H, d, J = 1.8 Hz), 13.40 (1H, bs)

EXAMPLE I-19

*N*1-[3-(3-Fluorophenyl)-1*H*-5-indazolyl]-2,2,2-trifluoro-1-ethanesulfonamide

A total of 26 mg of the title compound was obtained as a colorless powder by the procedure of Example I-18, except from 50 mg of *tert*-butyl 5-amino-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate produced in Production Example I-26 and 0.02 ml of 2,2,2-trifluoro-1-ethanesulfonyl chloride as starting materials.

^{1}H-NMR(400MHz, DMSO-d_6) δ 4.48 (2H, q, J = 10.0 Hz), 7.24 (1H, dt, J = 2.6, 8.0 Hz), 7.31 (1H, dd, J = 1.8, 8.9 Hz), 7.58 (1H, dt, J = 5.8, 8.0), 7.61 (1H, d, J = 8.9 Hz), 7.67 (1H, ddd, J = 1.5, 2.6, 10.1 Hz), 7.76 (1H, d, J = 8.0 Hz), 7.87 (1H, d, J = 1.8 Hz), 10.29 (1H, bs), 13.42 (1H, s)

EXAMPLE I-20

*N*1-[3-(3-Fluorophenyl)-1*H*-5-indazolyl]-4-methyl-1-

benzenesulfonamide

A total of 35 mg of the title compound was obtained as a colorless powder by the procedure of Example I-18, except from 50 mg of *tert*-butyl 5-amino-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate produced in Production Example I-26 and 30 mg of p-toluenesulfonyl chloride as starting materials.

^{1}H-NMR(400MHz, DMSO-d_6) δ 2.28 (3H, s), 7.15 (1H, dd, J = 1.8, 9.1 Hz), 7.20-7.27 (1H, m), 7.30 (2H, d, J = 8.8 Hz), 7.48 (2H, d, J = 8.8 Hz), 7.55-7.60 (5H, m), 10.03 (1H, bs), 13.35 (1H, s)

EXAMPLE I-21

*N*4-[3-(3-Fluorophenyl)-1*H*-5-indazolyl]-4-morpholinecarboxamide

A total of 30 mg of the title compound was obtained as a colorless powder by the procedure of Example I-18, except from 50 mg of *tert*-butyl 5-amino-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate produced in Production Example I-26 and 30 mg of 4-morpholinecarbonyl chloride as starting materials.

^{1}H-NMR(400MHz, DMSO-d_6) δ 3.40-3.47 (4H, m), 3.58-3.63 (4H, m), 7.21 (1H, dt, J = 2.7, 8.5 Hz), 7.48 (1H, d, J = 8.8 Hz), 7.53 (1H, dd, J = 1.4, 8.8), 7.56 (1H, dt, J = 6.5, 8.0 Hz), 7.65 (1H, ddd, J = 1.6, 2.7, 10.7 Hz), 7.76 (1H, d, J = 8.0 Hz), 8.14 (1H, d, J = 1.4 Hz), 8.59 (1H, s), 13.21 (1H, s)

EXAMPLE I-22

*N*1-[(1*R*)-2-Hydroxy-1-phenylethyl]-(*E*)-3-[3-(3-fluorophenyl)-1*H*-5-indazolyl]-2-propenamide

A total of 11 mg of the title compound was obtained as a colorless powder by the procedure of Example I-7, except from 50 mg of (*E*)-[3-(3-fluorophenyl)-1*H*-5-indazolyl]-2-propenoic acid produced in Production Example I-25 and 18 mg of S(+)-2-phenylglycinol as starting materials.

^{1}H-NMR(400MHz, DMSO-d_6) δ 3.61 (2H, t, J = 5.5 Hz), 4.93 (1H, t, J = 5.5 Hz), 4.98 (1H, dt, J = 5.5, 8.1 Hz), 6.81 (1H, d, J = 15.6 Hz), 7.20-7.25 (1H, m), 7.24 (1H, dt, J = 2.6, 8.6 Hz), 7.28-7.36 (4H, m), 7.56 (1H, dt, J = 6.0, 7.9 Hz), 7.55 (1H, dt, J = 7.9, 6.2 Hz), 7.62 (1H, d, J = 15.6 Hz), 7.63 (1H, d, J = 9.0 Hz), 7.65 (1H, d, J = 9.0 Hz), 7.78 (1H, ddd, J = 1.6, 2.3, 10.7 Hz), 7.89 (1H, d, J = 7.9 Hz), 8.30 (1H, s), 8.44 (1H, d, J = 8.1 Hz), 13.50 (1H, s)

EXAMPLE I-23

a; 3-(3-Fluorophenyl)-5-{[(3S)tetrahydro-3-furanyloxy]methyl}-1-trityl-1*H*-indazole

To a solution of 40 mg of (S)-3-hydroxytetrahydrofuran in tetrahydrofuran was added 15 mg of 60% sodium hydride (oily) in an atmosphere of nitrogen gas, and the mixture was stirred at room temperature for 15 minute. To the reaction mixture were added 150 mg of 5-(chloromethyl)-3-(3-fluorophenyl)-1-trityl-1*H*-indazole produced in Production Example I-32 and 45 mg of sodium iodide, followed by stirring at room temperature for five days. After adding water to the reaction mixture, it was extracted with 20 ml of ethyl acetate. The organic layer was sequentially washed with half-saturated aqueous sodium

chloride solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The resulting crude product was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 0:1 to 1:9), to give 84 mg of the title compound as a white amorphous powder.

^{1}H-NMR (400 MHz, DMSO-D6) δ 1.90-1.97 (2H, m), 3.63-3.77 (4H, m), 4.19-4.25 (1H, m), 4.50 (1H, d, J = 15.6 Hz), 4.52 (1H, d, J = 15.6 Hz), 6.46 (1H, d, J = 8.8 Hz), 7.09 (1H, d, J = 8.8Hz), 7.17-7.40 (16H, m), 7.56 (1H, td, J = 8.0, 6.4 Hz), 7.59 (1H, d, J = 10.0 Hz), 7.75 (1H, d, J = 8.0 Hz), 8.04 (1H, s).

b: 3-(3-Fluorophenyl)-5-{[(3*S*)tetrahydro-3-furanyloxy]methyl}-1*H*-indazole

To a solution of 82 mg of 3-(3-fluorophenyl)-5-{[(3*S*)tetrahydro-3-furanyloxy]methyl}-1-trityl-1*H*-indazole in 1.6 ml methylene chloride were added 0.05 ml of triisopropylsilane and 0.4 ml of trifluoroacetic acid, and the mixture was stirred at room temperature for 20 minutes. To the reaction mixture was added ethyl acetate. The mixture was sequentially washed with saturated aqueous sodium hydrogencarbonate solution (x2) and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. Then, the resulting crude product was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 1:4), to give 36 mg of the title compound as a viscous colorless oil.

^{1}H-NMR (400 MHz, DMSO-D6) δ 1.93-2.01 (2H, m), 3.64-3.81 (4H, m), 4.21-4.28 (1H, m), 4.59 (1H, d, J = 15.6 Hz), 4.62 (1H, d, J = 15.6 Hz), 7.24 (1H, td, J = 8.0, 2.4 Hz), 7.40 (1H, d, J = 8.4 Hz), 7.58 (1H, td, J = 8.0, 6.4 Hz), 7.59 (1H, d, J = 8.4 Hz), 7.74 (1H, ddd, J = 10.4, 1.6, 2.4 Hz), 7.86 (1H, d, J = 8.0 Hz), 8.04 (1H, s), 13.38 (1H, s).

EXAMPLE I-24

N-Ethyl-N'-[3-(3-fluorophenyl)-1*H*-5-indazolyl]urea

To a solution of 50 mg of *tert*-butyl 5-amino-3-(3-fluorophenyl)-1*H*-1-indazolecarboxylate produced in Production Example I-26 in 5 ml tetrahydrofuran was added 0.015 ml of ethyl isocyanate, and the mixture was stirred at room temperature for 2 hours. After the completion of the reaction, to the reaction mixture was added with 1 ml of 5 N hydrochloric acid and the mixture was stirred for further 1 hour. To the reaction mixture was added an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The extract was sequentially washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. To the residue was added diisopropyl ether, and the mixture was filtered, to give 28 mg of the title compound as a colorless powder.

^{1}H-NMR(400MHz, DMSO-d_6) δ 1.05 (3H, t, J = 6.5 Hz), 3.11 (2H, dq, J = 5.6, 6.5 Hz), 6.06 (1H, t, J = 5.6 Hz), 7.21 (1H, dt, J = 2.9, 8.6 Hz), 7.30 (1H, dd, J = 1.7, 8.9), 7.46 (1H, d, J = 8.9 Hz), 7.56 (1H, dt, J = 6.0, 8.1 Hz), 7.64 (1H, ddd, J = 1.4, 2.9, 10.6 Hz), 7.74 (1H, d, J

= 8.6 Hz), 8.22 (1H, s), 8.48 (1H, s), 13.17 (1H, s)

EXAMPLE I-25

a; [3-(3-Fluorophenyl)-1-(methoxymethyl)-1*H*-5-indazolyl](2-thienyl)methanol

A total of 700 mg of 3-(3-fluorophenyl)-1-(methoxymethyl)-1*H*-5-indazolylcarboxaldehyde was obtained as a colorless oil, by subjecting 780 mg of [3-(3-fluorophenyl)-1-(methoxymethyl)-1*H*-5-indazolyl]methanol produced in Production Example I-34 to the oxidation procedure of Production Example I-4-c.

A solution of 0.15 ml of thiophene in dry tetrahydrofuran was cooled to -78°C in an atmosphere of nitrogen gas, 1.8 ml of a 2.5 M solution of n-butyllithium in hexane was added dropwise, and the mixture was stirred at -20°C for 1 hour. The reaction mixture was cooled again to -78°C, and a solution of 0.35 g of the above-obtained 3-(3-fluorophenyl)-1-(methoxymethyl)-1*H*-5-indazolylcarboxaldehyde in 4 ml dry tetrahydrofuran was added to the reaction mixture, followed by heating to room temperature. To the reaction mixture was added an aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:6), to give 90 mg of the title compound

as a colorless oil.

^{1}H-NMR(400MHz,$CDCl_3$) δ 3.37 (3H, s), 5.74 (2H, s), 6.24 (1H, s), 6.92 (1H, dd, J = 1.0, 3.4 Hz), 6.95 (1H, dd, J = 3.4, 4.8 Hz), 7.11 (1H, dt, J = 2.7, 8.2 Hz), 7.28 (1H, dd, J = 1.0, 4.8 Hz), 7.48 (1H, dt, J = 6.5, 8.2 Hz), 7.54 (1H, dd, J = 1.9, 9.0 Hz), 7.60 (1H, d, J = 9.0 Hz), 7.69 (1H, ddd, J = 1.2, 2.7, 9.9 Hz), 7.76 (1H, dt, J = 1.2, 8.2 Hz), 8.12 (1H, d, J = 1.9 Hz)

b; [3-(3-Fluorophenyl)-1*H*-5-indazolyl](2-thienyl)methanone

A total of 90 mg of [3-(3-fluorophenyl)-1-(methoxymethyl)-1*H*-5-indazolyl](2-thienyl)methanol was oxidized by the procedure of Production Example I-4-c, to give 85 mg of [3-(3-fluorophenyl)-1-(methoxymethyl)-1*H*-5-indazolyl](2-thienyl)methanone as a colorless powder. This compound was dissolved in 3 ml of tetrahydrofuran, and 1 ml of 5 N hydrochloric acid was added, followed by heating under reflux for one day. To the reaction mixture was added aqueous sodium hydrogencarbonate solution and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:5), to give 30 mg of the title compound as colorless needles.

By treating 17 mg of [3-(3-fluorophenyl)-1-(hydroxymethyl)-1*H*-5-indazolyl](2-thienyl)methanone, a by-product formed by incomplete deprotection in the above

reaction, with concentrated aqueous ammonia solution in methanol, 11 mg of the title compound was further obtained.

^{1}H-NMR(400MHz, $CDCl_3$) δ 7.15 (1H, dt, J = 2.6, 8.4 Hz), 7.21 (1H, dd, J = 3.8, 4.9 Hz), 7.50 (1H, dt, J = 6.6, 8.0 Hz), 7.64 (1H, d, J = 8.9 Hz), 7.67-7.72 (1H, m), 7.71 (1H, dd, J = 1.0, 3.8 Hz), 7.74-7.79 (1H, m), 7.76 (1H, dd, J = 1.0, 4.9 Hz), 8.02 (1H, dd, J = 1.4, 8.9 Hz), 8.61 (1H, d, J = 1.4 Hz)

EXAMPLE I-26

a; *tert*-Butyl 3-(3-fluorophenyl)-5-[hydroxy(phenyl)methyl]-1*H*-1-indazolecarboxylate

A total of 30 mg of the title compound was obtained as a colorless oil by the procedure of Production Example I-25-a, except from 160 mg of *tert*-butyl 3-(3-fluorophenyl)-5-formyl-1*H*-1-indazolecarboxylate produced in Production Example I-25-a and 0.58 ml of a 1.04 N solution of phenyllithium in cyclohexane as starting materials.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.73 (9H, s), 6.02 (1H, bs), 6.24 (1H, s), 7.17 (1H, ddt, J = 1.3, 2.7, 8.5 Hz), 7.25-7.30 (1H, m), 7.32-7.37 (2H, m), 7.37-7.41 (2H, m), 7.49 (1H, dt, J = 6.3, 7.8 Hz), 7.51 (1H, dd, J = 1.5, 8.6 Hz), 7.72 (1H, ddd, J = 1.7, 2.7, 9.7 Hz), 7.88 (1H, dd, J = 1.3, 7.8 Hz), 8.06 (1H, d, J = 1.5 Hz), 8.13 (1H, d, J = 8.6 Hz)

b; [3-(3-Fluorophenyl)-1*H*-5-indazolyl](phenyl)methanone

A total of 30 mg of *tert*-butyl 3-(3-fluorophenyl)-5-[hydroxy(phenyl)methyl]-1*H*-1-indazolecarboxylate as a starting material was oxidized by the procedure of Production Example I-4-c, was treated with 5 N hydrochloric

acid by the procedure of Production Example I-25-b, to give 4 mg of the title compound as a colorless powder.

^{1}H-NMR(400MHz, DMSO-d_6) δ 7.25 (1H, ddt, J = 0.7, 2.7, 8.6 Hz), 7.52-7.59 (3H, m), 7.64-7.70 (1H, m), 7.69 (1H, ddd, J = 1.4, 2.7, 10.4 Hz), 7.74 (1H, dd, J = 0.7, 8.6 Hz), 7.75-7.80 (3H, m, 7.83 (1H, dd, J = 1.5, 8.6 Hz), 8.38 (1H, dd, J = 0.7, 1.5 Hz)

EXAMPLE I-27

a; (*E*)-3-(Dimethylamino)-1-(1*H*-3-indazolyl)-2-propen-1-one

A total of 5.0 g of 1*H*-indazole as a starting material was subjected to bromination and *tert*-butoxycarbonylation by the procedures of Production Examples I-26-a and I-26-b, was acetylated at the 3-position by the procedure of Production Example I-29-a, to give 2.5 g of *tert*-butyl 3-acetyl-1*H*-1-indazolecarboxylate. A total of 1.5 g of this product was treated with 5 N hydrochloric acid by the procedure of Production Example I-25-b and thereby yielded 860 mg of 1-(1*H*-3-indazolyl)ethanone. A solution of 240 mg of this product and 0.4 ml of *N,N*-dimethylformamide dimethylacetal in 5 ml toluene was heated under reflux for 9 hours. The solvent was evaporated, and the residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 2:1), to give 88 mg of the title compound as a colorless powder.

^{1}H-NMR(400MHz, DMSO-d_6) δ 2.88 (3H, bs), 3.13 (3H, bs), 6.08 (1H, d, J = 13.1 Hz), 7.19 (1H, t, J = 7.6 Hz), 7.36 (1H, t, J = 7.6 Hz), 7.56 (1H, d, J = 7.6 Hz), 7.72 (1H, d, J = 13.1 Hz), 8.26 (1H, d, J = 7.6 Hz),

13.37 (1H, s)

b; 4-(1*H*-3-Indazolyl)-2-pyrimidinamine

A total of 20 mg of metallic sodium was dissolved in 5 ml of dry ethanol. To the resulting solution were added 76 mg of guanidine hydrochloride and 85 mg of (*E*)-3-(dimethylamino)-1-(1*H*-3-indazolyl)-2-propen-1-one, followed by heating under reflux for 12 hours. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 7:5), to give 55 mg of the title compound as a colorless powder.

^{1}H-NMR(400MHz, DMSO-d_6) δ 6.69 (2H, bs), 7.22 (1H, t, J = 7.9 Hz), 7.24 (1H, d, J = 5.3 Hz), 7.40 (1H, t, J = 7.9 Hz), 7.58 (1H, d, J = 7.9 Hz), 8.26 (1H, d, J = 5.3 Hz), 8.67 (1H, d, J = 7.9 Hz)

The compounds according to Examples I-28 to I-100 were synthesized by the following Synthesis Process I-A.

Synthesis Process I-A

A total of 96 pieces of a polystyrene resin (SunPhase Polystyrene D-Seriese, Trityl™) labeled with TRANSTEM™ was left stand in 100 ml of a 10% solution of acetyl chloride in methylene chloride for 3 hours. After removing the solution, the residue was washed with three portions of methylene chloride and dried in vacuo. The resin was

heated in a solution of 15 g of 3-bromo-5-nitro-1*H*-indazole produced in Production Example I-26-a and diisopropylamine in 150 ml N-methylpyrrolidone at 80°C for 4 hours. After removing the solution, the resin was sequentially washed with N-methylpyrrolidone, ethanol, water, methanol and tetrahydrofuran, and dried in vacuo.

The resulting resin was divided among 8 groups (each 12 pieces) according to its label and was added to 15 ml of a solution of 0.5 M boronic acid in N-methylpyrrolidone of eight types previously prepared, respectively. Each reaction mixture was treated with 1.5 ml of a 0.5 M solution of 2-(di-*tert*-butylphosphino)biphenyl in N-methylpyrrolidone, 1.8 ml of a 8 M aqueous solution of potassium fluoride, and a catalytic amount of palladium(II) acetate by heating at 80°C for 12 hours. After removing the solution, the resin was washed according to the above procedure and was dried under reduced pressure. The resin was heated in 150 ml of a 2 M solution of stannic chloride in N-methylpyrrolidone at 80°C for 4 hours. After removing the solution, the resin was washed according to the above procedure and was dried in vacuo.

The resin was further divided among 12 groups (each 8 pieces) according to its label and was added to 15 ml of a solution of 0.5 M carboxylic acid in N-methylpyrrolidone of twelve types previously prepared, respectively. To each well were sequentially added 1.15 g of 1-

hydroxybenzotriazole monohydrate, 1.2 ml of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (= WSC) and 2.0 ml of diisopropylethylamine. In a sulfonamide compound, a sulfonyl chloride reagent and diisopropylethylamine were added in tetrahydrofuran. The mixture was subjected to sonication for 1 hour and was left stand at room temperature for one day. After removing the solution, the resin was washed according to the above procedure and was dried under reduced pressure. The resin was placed in each of 96-well pin plate according to its label.

A mixture solution of 0.5 ml of trifluoroacetic acid, 0.1 ml of triisopropylsilane, and 0.5 ml of dichloromethane previously prepared was added to the resin in each of the 96-well plate, and the mixture was subjected to sonication for 10 minutes and was left stand for 30 minutes. This procedure was repeated twice, and the resin was washed with 1 ml of dimethylformamide. Next, nitrogen gas was blown to the acid-treated wells, and each residue was dissolved in a dimethylformamide solution obtained in washing procedure, was purified and separated by LC-MS (developing solvent (eluent); 0.1% solution of trifluoroacetic acid in acetonitrile:0.1% aqueous solution of trifluoroacetic acid = 1:99 to 100:0/20 minute-cycle, flow rate; 20 ml/min, column; YMC Combiprep ODS-AM, 20 mmΦ x 50 mm (Long)), to give the following compounds.

EXAMPLE I-28

2-(5-{[2-(1,1-Dioxo-1l^6,4-thiazinan-4-yl)acetyl]amino}-1*H*-3-indazolyl)benzoic acid

MS (ESI)m/z 429 MH$^+$

EXAMPLE I-29

*N*7-[3-(2,3-Dihydro-1*H*-5-indolyl)-1*H*-5-indazolyl]bicyclo[4.2.0]octa-1(6),2,4-triene-7-carboxamide

MS (ESI)m/z 381 MH$^+$

EXAMPLE I-30

*N*1-[3-(8-Quinolyl)-1*H*-5-indazolyl]-2,4-dichlorobenzamide

MS (ESI)m/z 433 M$^+$

EXAMPLE I-31

*N*1-{3-[4-(Methylsulfonyl)phenyl]-1*H*-5-indazolyl}-2-(2,4-dichlorophenyl)acetamide

MS (ESI)m/z 474 M$^+$

EXAMPLE I-32

*N*1-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)-1-cyclopentanecarboxamide

MS (ESI)m/z 362 MH$^+$

EXAMPLE I-33

*N*7-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)-2,3-dihydrobenzo[*b*]furan-7-carboxamide

MS (ESI)m/z 412 MH$^-$

EXAMPLE I-34

*N*1-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)-3-(2-thienyl)propanamide

MS (ESI)m/z 404 MH$^+$

EXAMPLE I-35

*N*1-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)-(*E*)-3-cyclopropyl-2-propenamide

MS (ESI)m/z 360 MH+

EXAMPLE I-36

*N*1-[3-(2-Naphthyl)-1*H*-5-indazolyl]-1-cyclopropanecarboxamide

MS (ESI)m/z 328 MH+

EXAMPLE I-37

*N*2-[3-(2-Naphthyl)-1*H*-5-indazolyl]-2-thiophenecarboxamide

MS (ESI)m/z 370 MH+

EXAMPLE I-38

*N*1-[3-(2-Naphthyl)-1*H*-5-indazolyl]-8-hydroxyoctanamide

MS (ESI)m/z 402 MH+

EXAMPLE I-39

*N*1-(3-(3-[(Cyclopropylcarbonyl)amino]phenyl)-1*H*-5-indazolyl)-1-cyclopropanecarboxamide

MS (ESI)m/z 361 MH+

EXAMPLE I-40

*N*1-3-[4-(Benzyloxy)phenyl]-1*H*-5-indazolyl3-oxo-1-cyclopentanecarboxamide

MS (ESI)m/z 426 MH+

EXAMPLE I-41

*N*1-[3-(2-Naphthyl)-1*H*-5-indazolyl]-4-(hydroxymethyl)benzamide

MS (ESI)m/z 394 MH+

EXAMPLE I-42

*N*1-[3-(2-Naphthyl)-1*H*-5-indazolyl]-4-methoxy-1-cyclohexanecarboxamide

MS (ESI)m/z 400 MH^+

EXAMPLE I-43

*N*1-[3-(2-Naphthyl)-1*H*-5-indazolyl]-2-hydroxy-3-phenylpropanamide

MS (ESI)m/z 408 MH^+

EXAMPLE I-44

*N*1-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)-*trans*-4-hydroxy-1-cyclohexanecarboxamide

MS (ESI)m/z 392 MH^+

EXAMPLE I-45

*N*1-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)-2-(3-pyridyl)acetamide

MS (ESI)m/z 369 MH^+

EXAMPLE I-46

*N*1-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)-2-(3-thienyl)acetamide

MS (ESI)m/z 374 MH^+

EXAMPLE I-47

*N*2-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)-1,2,3,4-tetrahydro-2-naphthalenecarboxamide

MS (ESI)m/z 408 MH^+

EXAMPLE I-48

*N*2-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)-2-furamide

MS (ESI)m/z 344 MH^+

EXAMPLE I-49

*N*3-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)-3-furamide

MS (ESI)m/z 344 MH^+

EXAMPLE I-50

*N*1-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)-2-hydroxy-2-phenylacetamide

MS (ESI)m/z 384 MH^+

EXAMPLE I-51

*N*1-[3-(4-Acetylphenyl)-1*H*-5-indazolyl]-2-(2-pyridyl)acetamide

MS (ESI)m/z 371 MH^+

EXAMPLE I-52

*N*1-[3-(4-Acetylphenyl)-1*H*-5-indazolyl]-2-(3,4-dimethoxyphenyl)acetamide

MS (ESI)m/z 430 MH^+

EXAMPLE I-53

*N*1-[3-(2-Naphthyl)-1*H*-5-indazolyl]-4-oxopentanamide

MS (ESI)m/z 358 MH^+

EXAMPLE I-54

*N*1-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)-3-methoxypropanamide

MS (ESI)m/z 352 MH^+

EXAMPLE I-55

*N*3-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)tetrahydro-3-furancarboxamide

MS (ESI)m/z 364 MH^+

EXAMPLE I-56

*N*1-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)-3-oxo-1-indancaroxamide

MS (ESI)m/z 408 MH^+

EXAMPLE I-57

*N*1-[3-(4-Acetylphenyl)-1*H*-5-indazolyl]-3-phenoxypropanamide

MS (ESI)m/z 400 MH^+

EXAMPLE I-58

*N*1-[3-(2-Naphthyl)-1*H*-5-indazolyl]-3-hydroxy-2-(hydroxymethyl)-2-methylpropanamide

MS (ESI)m/z 376 MH^+

EXAMPLE I-59

*N*1-[3-(2-Naphthyl)-1*H*-5-indazolyl]-2-(2-oxocyclopentyl)acetamide

MS (ESI)m/z 384 MH^+

EXAMPLE I-60

*N*2-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)-(2*S*)-5-oxotetrahydro-1*H*-2-pyrrolecarboxamide

MS (ESI)m/z 377 MH^+

EXAMPLE I-61

*N*2-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)-(2*R*)-5-oxotetrahydro-1*H*-2-pyrrolecarboxamide

MS (ESI)m/z 377 MH^+

EXAMPLE I-62

*N*2-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)tetrahydro-2-

furancarboxamide

MS (ESI)m/z 348 MH+

EXAMPLE I-63

*N*3-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)-2,2-dimethyl-5-oxotetrahydro-3-furancarboxamide

MS (ESI)m/z 390 MH+

EXAMPLE I-64

N-(3-Phenyl-1*H*-5-indazolyl)methanesulfonamide

MS (ESI)m/z 288 MH+

EXAMPLE I-65

4-({[3-(3-Fluorophenyl)-1*H*-5-indazolyl]amino}sulfonyl)benzoic acid

MS (ESI)m/z 412 MH+

EXAMPLE I-66

*N*1-[5-({[3-(3-Fluorophenyl)-1*H*-5-indazolyl]amino}sulfonyl)-4-methyl-1,3-thiazol-2-yl]acetamide

MS (ESI)m/z 446 MH+

EXAMPLE I-67

*N*2-[3-(4-Methoxyphenyl)-1*H*-5-indazolyl]-4-(phenylsulfonyl)-2-thiphenesulfonamide

MS (ESI)m/z 526 MH+

EXAMPLE I-68

*N*2-[3-(1,3-Benzodioxol-5-yl)-1*H*-5-indazolyl]-2-propanesulfonamide

MS (ESI)m/z 360 MH+

EXAMPLE I-69

N1-[3-(2-Thienyl)-1*H*-5-indazolyl]-3,5-di(trifluoromethyl)-1-benzenesulfonamide

MS (ESI)m/z 492 MH^+

EXAMPLE I-70

N,N-Dimethyl-*N'*-{3-[4-(trifluoromethyl)phenyl]-1*H*-5-indazolyl}sulfamide

MS (ESI)m/z 385 MH^+

EXAMPLE I-71

*N*2-{3-[3,5-Di(trifluoromethyl)phenyl]-1*H*-5-indazolyl}-5-(2-pyridyl)-2-thiophenesulfonamide

MS (ESI)m/z 569 MH^+

EXAMPLE I-72

*N*2-[3-(2,4-Dichlorophenyl)-1*H*-5-indazolyl]-2-furamide

MS (ESI)m/z 372 MH^+

EXAMPLE I-73

*N*1-[3-(3-Ethoxyphenyl)-1*H*-5-indazolyl]-3-hydroxy-3-methylpentanamide

MS (ESI)m/z 368 MH^+

EXAMPLE I-74

*N*1-(3-Dibenzo[*b,d*]furan-4-yl-1*H*-5-indazolyl)-1-cyclopropanecaroxamide

MS (ESI)m/z 368 MH^-

EXAMPLE I-75

*N*1-{3-[4-(*tert*-butyl)phenyl]-1*H*-5-indazolyl}-1-phenyl-1-cyclopropanecarboxamide

MS (ESI)m/z 410 MH^-

EXAMPLE I-76

*N*1-[3-(2-Naphthyl)-1*H*-5-indazolyl]-3-hydroxy-2,2-dimethylpropanamide

MS (ESI)m/z 360 MH^+

EXAMPLE I-77

*N*1-{3-[3-Fluoro-4-(phenyl)phenyl]-1H-5-indazolyl}-2-oxo-2-phenylacetamide

MS (ESI)m/z 436 MH^+

EXAMPLE I-78

*N*1-{3-[4-(trifluoromethoxy)phenyl]-1*H*-5-indazolyl}-4-(dimethylamino)benzamide

MS (ESI)m/z 441 MH^+

EXAMPLE I-79

*N*1-[3-(4-Phenoxyphenyl)-1*H*-5-indazolyl]-3-hydroxy-3-methylbutanamide

MS (ESI)m/z 402 MH^+

EXAMPLE I-80

*N*1-[3-(3,4-Dichlorophenyl)-1*H*-5-indazolyl]-(1*S*,2*S*)-2-phenylcyclopropane-1-carboxamide

MS (ESI)m/z 422 M^+

EXAMPLE I-81

*N*7-[3-(3-Acetylphenyl)-1*H*-5-indazolyl]bicyclo[4.2.0]octa-1(6),2,4-triene-7-carboxamide

MS (ESI)m/z 382 MH^+

EXAMPLE I-82

*N*4-[3-(3-Acetylphenyl)-1*H*-5-indazolyl]isonicotinamide

MS (ESI)m/z 357 MH^+

EXAMPLE I-83

*N*1-[3-(3-Acetylphenyl)-1*H*-5-indazolyl]-(2*R*)-2-amino-2-cyclohexylethanamide

MS (ESI)m/z 391 MH^+

EXAMPLE I-84

*N*1-[3-(5-Acetyl-2-thienyl)-1*H*-5-indazolyl]-1-cyclobutanecarboxamide

MS (ESI)m/z 340 MH^+

EXAMPLE I-85

*N*1-[3-(4-Biphenyl)-1*H*-5-indazolyl]-1-phenyl-1-cyclopentanecarboxamide

MS (ESI)m/z 458 MH^+

EXAMPLE I-86

*N*3-[3-(3-Biphenyl)-1*H*-5-indazolyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide

MS (ESI)m/z 445 MH^-

EXAMPLE I-87

*N*1-{3-[3,5-Di(trifluoromethyl)phenyl}-1*H*-5-indazolyl}-(2*R*)-2-amino-3,3-diphenylpropanamide

MS (ESI)m/z 569 MH^+

EXAMPLE I-88

*N*1-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)-(2*R*)-2-amino-3,3-dimethylbutanamide

MS (ESI)m/z 363 MH^+

EXAMPLE I-89

*N*1-(3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl)-(2*R*)-2-amino-3-

(benzyloxy)propanamide

MS (ESI)m/z 427 MH$^+$

EXAMPLE I-90

*N*1-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)-(2*R*)-2-amino-3-phenylpropanamide

MS (ESI)m/z 413 MH$^+$

EXAMPLE I-91

*N*1-(3-Benzo[*b*]thiophen-2-yl-1*H*-5-indazolyl)-(2*R*)-2-amino-3-methylbutanamide

MS (ESI)m/z 365 MH$^+$

EXAMPLE I-92

*N*2-[3-(2-Thienyl)-1*H*-5-indazolyl]-2-pyridinecarboxamide

MS (ESI)m/z 321 MH$^+$

EXAMPLE I-93

*N*1-[3-(2-Furyl)-1*H*-5-indazolyl]-3-hydroxy-2-phenylpropanamide

MS (ESI)m/z 348 MH$^+$

EXAMPLE I-94

N-[3-(2-Naphthyl)-1*H*-5-indazolyl]methanesulfonamide

MS (ESI)m/z 338 MH$^+$

EXAMPLE I-95

*N*1-[3-(2-Naphthyl)-1*H*-5-indazolyl]acetamide

MS (ESI)m/z 302 MH$^+$

EXAMPLE I-96

*N*1-{3-[2-(trifluoromethyl)phenyl]-1*H*-5-indazolyl}-2-(1,3-benzodioxol-5-yl)acetamide

MS (ESI)m/z 440 MH^+

EXAMPLE I-97

*N*1-[3-(3-Thienyl)-1*H*-5-indazolyl]-2-methoxyacetamide

MS (ESI)m/z 288 MH^+

EXAMPLE I-98

*N*1-[3-(1*H*-2-Pyrrolyl)-1*H*-5-indazolyl]-(3*S*)-3-hydroxy-3-phenylpropanamide

MS (ESI)m/z 347 MH^+

EXAMPLE I-99

*N*1-[3-(2,4-Dimethoxy-5-pyrimidinyl)-1*H*-5-indazolyl]-2-(2-thienyl)acetamide

MS (ESI)m/z 396 MH^+

EXAMPLE I-100

*N*1-[3-(3-Pyridyl)-1*H*-5-indazolyl]-(3*R*)-3-hydroxy-3-phenylpropanamide

MS (ESI)m/z 359 MH^+

The compounds according to Examples I-101 to I-107 were synthesized by the following Synthesis Process I-B.

Synthesis Process I-B

The resin was subjected to the procedures of Synthesis Process I-A till the treatment with stannic chloride and was divided among two groups (each 48 pieces) according to the label, followed by amidation with a 0.5 M solution of any of two amino acids having an amino group protected by Fmoc group in N-methylpyrrolidone. Each of the resin was washed and was treated with N-methylpyrrolidone solution

containing 20% piperidine to thereby remove the Fmoc group.

The resulting resin was divided among twelve groups (each 8 pieces), ten groups of which were treated with any of 0.5 M solution of five alkyl bromides in N-methylpyrrolidone and cesium carbonate for alkylation of the amide group. Then, the resin was subjected to an acid treatment according to the procedure of Synthesis Process I-A, was separated and purified by LC-MS according to the procedure of Synthesis Process I-A, to give the following compounds.

EXAMPLE I-101

*N*2-[3-Benzo[*b*]furan-2-yl-1*H*-5-indazolyl]-(2*S*)-tetrahydro-1*H*-2-pyrrolecarboxamide

MS (ESI)m/z 347 MH^+

EXAMPLE I-102

*N*2-[3-(5-Acetyl-2-thienyl)-1*H*-5-indazolyl]-(2*S*)-1-benzyltetrahydro-1*H*-2-pyrrolecarboxamide

MS (ESI)m/z 445 MH^+

EXAMPLE I-103

*N*2-[3-(3-Ethoxyphenyl)-1*H*-5-indazolyl]-(2*S*)-1-[3-(trifluoromethyl)benzyl]tetrahydro-1*H*-2-pyrrolecarboxamide

MS (ESI)m/z 509 MH^+

EXAMPLE I-104

*N*4-[3-(2-Naphthyl)-1*H*-5-indazolyl]-4-piperidinecarboxamide

MS (ESI)m/z 371 MH^+

EXAMPLE I-105

N4-[3-Benzo[b]thiophen-2-yl-1H-5-indazolyl]-1-benzyl-4-piperidinecarboxamide

MS (ESI)m/z 467 MH^+

EXAMPLE I-106

N4-[3-(4-Acetylphenyl)-1H-5-indazolyl]-1-(2,4-difluorobenzyl)-4-piperidinecarboxamide

MS (ESI)m/z 489 MH^+

EXAMPLE I-107

Methyl {3-[4-({[3-(1-naphthyl)-1H-5-indazolyl]amino}carbonyl)piperidino]methyl}benzoate

MS (ESI)m/z 519 MH^+

The compounds according to Examples I-108 to I-156 were synthesized by the following Synthesis Process I-C.

Synthesis Process I-C

A solution of 180 mg of each indazolecarboxylic acid produced in Production Examples I-1 to I-25 in 6 ml dimethylformamide was pipetted into several test tubes in an amount of 0.5 ml each, each of which was treated with 1.1 equivalents of any of various amines. The reaction mixture was sequentially treated with 0.065 ml of a 1 M solution of 1-hydroxybenzotriazole monohydrate in dimethylformamide, 0.130 ml of a 1 M solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (= WSC) in dimethylformamide, and 0.05 ml of diisopropylamine, the mixture was subjected to sonication for 10 minutes and was left stand for one day. Each of the reaction mixtures was

separated and purified by LC-MS under the conditions of Synthesis Process I-A and thereby yielded the test compounds.

EXAMPLE I-108

[3-(3-Fluorophenyl)-1*H*-5-indazolyl](morpholino)methanone

MS (ESI)m/z 326 MH^+

EXAMPLE I-109

[3-(3-Fluorophenyl)-1*H*-5-indazolyl](4-methylpiperazino)methanone

MS (ESI)m/z 339 MH^+

EXAMPLE I-110

[3-(3-Fluorophenyl)-1*H*-5-indazolyl](4-hydroxy-4-phenylpiperidino)methanone

MS (ESI)m/z 416 MH^+

EXAMPLE I-111

*N*5-(3-morpholinopropyl)-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 383 MH^+

EXAMPLE I-112

*N*5-[(1*S*)-1-(Hydroxymethyl)-3-methylbutyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 342 MH^+

EXAMPLE I-113

*N*5-[(1*S*)-2-Hydroxy-1-(1*H*-1-indazolylmethyl)ethyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 380 MH^+

EXAMPLE I-114

*N*5-[(1*S*)-1-Benzyl-2-hydroxyethyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 390 MH^+

EXAMPLE I-115

*N*5-[(1*S*)-1-(Hydroxymethyl)propyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 328 MH^-

EXAMPLE I-116

*N*5-[(1*R*)-1-(Hydroxymethyl)propyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 328 MH^+

EXAMPLE I-117

*N*5-(2-Piperidinoethyl)-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 367 MH^+

EXAMPLE I-118

*N*5-(*trans*-4-Hydroxycyclohexyl)-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 354 MH^+

EXAMPLE I-119

*N*5-[2-(2-Hydroxyethoxy)ethyl]-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 344 MH^+

EXAMPLE I-120

*N*5-Ethyl-*N*5-(2-hydroxyethyl)-3-(3-fluorophenyl)-1*H*-5-

indazolecarboxamide

MS (ESI)m/z 328 MH+

EXAMPLE I-121

*N*5-[4-(Aminosulfonyl)benzyl]-3-(2-methoxyphenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 437 MH+

EXAMPLE I-122

*N*5-[(1*R*,2*R*)-2-(Hydroxymethyl)cyclohexyl]-3-(2-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 368 MH+

EXAMPLE I-123

*N*5-[(1*R*,2*R*)-2-Hydroxycyclohexyl]-3-(2-quinolyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 387 MH+

EXAMPLE I-124

*N*5-[(1-(Methoxymethyl)propyl]-3-(2-quinolyl)1*H*-5-indazolecarboxamide

MS (ESI)m/z 375 MH-

EXAMPLE I-125

*N*5-[4-(Methylsulfonyl)benzyl]-3-(2-quinolyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 457 MH+

EXAMPLE I-126

*N*5-[(1*R*,2*S*)-2-(Hydroxymethyl)cyclohexyl]-3-(3-quinolyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 401 MH+

EXAMPLE I-127

*N*5-[2-(1*H*-3-Indolyl)ethyl]-3-(4-quinolyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 368 MH^+

EXAMPLE I-128

*N*5-(5-Hydroxypentyl)-3-(-(1,3-benzothiazol-2-yl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 381 MH^+

EXAMPLE I-129

*N*5-Cyclopropyl-3-phenyl-1*H*-5-indazolecarboxamide

MS (ESI)m/z 278 MH^+

EXAMPLE I-130

*N*5-[2-(Acetylamino)ethyl]-3-(2-naphthyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 373 MH^+

EXAMPLE I-131

*N*5-(3-Pyridylmethyl)-3-(5-acetyl2-thienyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 377 MH^+

EXAMPLE I-132

*N*5-[(1*S*)-2-Amino-1-methyl-2-oxoethyl]-3-(3-acetylphenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 373 $M+Na^+$

EXAMPLE I-133

*N*6-(3-Methoxybenzyl)-3-(3-fluorophenyl)-1*H*-6-indazolecarboxamide

MS (ESI)m/z 376 MH^+

EXAMPLE I-134

*N*7-[3-(1*H*-1-Imidazolyl)propyl]-3-(3-fluorophenyl)-1*H*-7-indazolecarboxamide

MS (ESI)m/z 364 MH^+

EXAMPLE I-135

*N*1-Cyclopropyl-2-[3-(3-fluorophenyl)-1*H*-5-indazolyl]acetamide

MS (ESI)m/z 310 MH^+

EXAMPLE I-136

*N*1-(3-Methoxyphenethyl)-2-[3-(3-fluorophenyl)-1*H*-5-indazolyl]acetamide

MS (ESI)m/z 404 MH^+

EXAMPLE I-137

*N*5-[3-(2-Oxotetrahydro-1*H*-1-pyrrolyl)propyl]-3-benzo[*b*]thiophen-2-yl-1*H*-5-indazolecarboxamide

MS (ESI)m/z 419 MH^-

EXAMPLE I-138

*N*5-[2-(2-Thienyl)ethyl]-3-benzo[*b*]thiophen-2-yl-1*H*-5-indazolecarboxamide

MS (ESI)m/z 404 MH^+

EXAMPLE I-139

*N*5-(2-Phenoxyethyl)-3-benzo[*b*]furan-2-yl-1*H*-5-indazolecarboxamide

MS (ESI)m/z 398 MH^+

EXAMPLE I-140

*N*5-(3-Tetrahydro-1*H*-1-pyrrolylpropyl)-3-benzo[*b*]furan-2-yl-1*H*-5-indazolecarboxamide

MS (ESI)m/z 389 MH^+

EXAMPLE I-141

*N*5-[2-(1*H*-3-Indolyl)ethyl]-3-(2-naphthyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 431 MH^+

EXAMPLE I-142

*N*5-(2,3-Dihydro-1*H*-2-indenyl))-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 372 MH^+

EXAMPLE I-143

*N*5-Cyclopropyl-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 296 MH^+

EXAMPLE I-144

*N*5-(2-Furylmethyl)-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 336 MH^-

EXAMPLE I-145

*N*5-Tetrahydro-2-furanylmethyl-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 340 MH^+

EXAMPLE I-146

*N*5-(2-Morpholinoethyl)-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 369 MH^+

EXAMPLE I-147

*N*5-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 390 MH^+

EXAMPLE I-148

*N*5-[(2*R*)-3,4-Dihydro-2*H*-2-chromenylmethyl]-3-(2-pyridyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 385 MH^+

EXAMPLE I-149

*N*5-[1-(Methoxymethyl)propyl]-3-(2-pyridyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 325 MH^+

EXAMPLE I-150

*N*5-(1,3-Benzodioxol-5-ylmethyl)-3-(3-pyridyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 373 MH^+

EXAMPLE I-151

*N*5-Cyclopropylmethyl-3-(2-naphthyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 342 MH^-

EXAMPLE I-152

*N*5-[(3*R*)-2-Oxotetrahydro-1*H*-3-furanyl]-3-(2-naphthyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 372 MH^+

EXAMPLE I-153

*N*5-[2-(2-Furyl)-2-oxoethyl]-3-(2-naphthyl)-1*H*-5-

indazolecarboxamide

MS (ESI)m/z 396 MH^+

EXAMPLE I-154

*N*5-[2-((1,3-Thiazol-2-yl)ethyl]-3-(2-naphthyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 399 MH^+

EXAMPLE I-155

*N*5-(2-Ethoxyethyl)-3-(3-fluorophenyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 328 MH^+

EXAMPLE I-156

*N*5-[(3*S*)-2-Oxotetrahydro-1*H*-3-furanyl]-3-(2-quinolyl)-1*H*-5-indazolecarboxamide

MS (ESI)m/z 373 MH^+

The compounds according to Examples I-157 to I-162 were synthesized by the following Synthesis Process I-D.

Synthesis Process I-D

Each of the amines produced in Production Examples I-27, I-28 and I-30 was dissolved in dimethylformamide to a concentration of 5 mg/ml and each 1 ml of the solution was pipetted into test tubes. The solution was mixed with 0.05 ml of a 0.5 M solution of any of carboxylic acids, 0.025 ml of a 1 M solution of 1-hydroxybenzotriazole monohydrate in dimethylformamide, and 0.05 ml of a 1 M solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (= WSC) in dimethylformamide, each of which had been prepared, and the

mixture was stirred at room temperature overnight. A sulfonamide compound was allowed to react with methanesulfonyl chloride in tetrahydrofuran in the presence of triethylamine. Each of the reaction mixtures was separated and purified by LC-MS under the conditions of Synthesis Process I-A, to give the following compounds.

EXAMPLE I-157

Benzyl N-((1*S*)-2-{[3-(3-fluorophenyl)-1*H*-6-indazolyl]amino}-1-methyl-2-oxoethyl)carbamate

MS (ESI)m/z 433 MH^+

EXAMPLE I-158

*N*1-[3-(3-Fluorophenyl)-1*H*-7-indazolyl]-3-phenoxybenzamide

MS (ESI)m/z 424 MH^+

EXAMPLE I-159

*N*1-{[3-(3-Fluorophenyl)-1*H*-5-indazolyl]methyl}-1-cyclopropanecarboxamide

MS (ESI)m/z 310 MH^+

EXAMPLE I-160

*N*1-{[3-(3-Fluorophenyl)-1*H*-5-indazolyl]methyl}-3-methoxybenzamide

MS (ESI)m/z 376 MH^+

EXAMPLE I-161

*N*1-{[3-(3-Fluorophenyl)-1*H*-5-indazolyl]methyl}-3-phenoxypropanamide

MS (ESI)m/z 390 MH^+

EXAMPLE I-162

N3-{[3-(3-Fluorophenyl)-1H-5-indazolyl]methyl}tetrahydro-3-furancarboxamide

MS (ESI)m/z 340 MH^+

The compounds according to Examples I-163 to I-166 were synthesized by according to following Synthesis Process I-E.

Synthesis Process I-E

Each of the amines produced in Production Examples I-29 and I-36 was dissolved in dimethylformamide to a concentration of 20 mg/ml and each 0.5 ml of the solution was pipetted into test tubes. The solution was sequentially mixed with 0.08 ml of a 0.5 M solution of any of carboxylic acids in dimethylformamide, 0.1 ml of a 0.5 M solution of 1-hydroxybenzotriazole monohydrate in dimethylformamide, 0.1 ml of a 1 M solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in dimethylformamide, and 0.05 ml of diisopropylethylamine, each of which had been prepared, and the mixture was left stand for one day. The reaction mixture in the test tube was diluted with water, was extracted with two portions of ethyl acetate and was air-dried by blowing nitrogen gas to remove the solvent. The resulting residue was treated with 1 ml of a 1:1 mixture of trifluoroacetic acid and dichloromethane containing 10% triethylsilane by standing still for 1 hour. The reaction mixture was air-dried by blowing nitrogen gas, and residue was dissolved in 0.5 ml of N,N-

dimethylformamide. Each of the solutions was separated and purified by LC-MS by the procedure of Synthesis Process I-A, to give the following compounds.

EXAMPLE I-163

N1-(3-Imidazo[1,2-*a*]pyridin-2-yl-1*H*-5-indazolyl)-2-(3-thienyl)acetamide

MS (ESI)m/z 374 MH^+

EXAMPLE I-164

N2-(3-Imidazo[1,2-*a*]pyridin-2-yl-1*H*-5-indazolyl)-1,2,3,4-tetrahydronaphthalene-2-carboxamide

MS (ESI)m/z 408 MH^+

EXAMPLE I-165

Cyclopropanecarboxylic acid [3-(fluorobenzo[*b*]furan-2-yl)-1*H*-indazol-5-yl]amide

MS (ESI)m/z 336 MH^+

EXAMPLE I-166

5-Oxo-pyrrolidine-(2S)-2-carboxylic acid [3-(fluorobenzo[*b*]furan-2-yl)-1*H*-indazol-5-yl]amide

MS (ESI)m/z 379 MH^+

The compounds according to Examples I-167 and I-168 were synthesized by following Synthesis Process I-F.

Synthesis Process I-F

As a starting material, 0.19 g of *tert*-butyl 3-(2-naphthyl)-5-(hydroxymethyl)-1*H*-1-indazolecarboxylate produced in Production Example I-33 was subjected to the procedures of Production Example I-30a and I-30b, to give

0.15 g of *tert*-butyl 5-(aminomethyl)-3-(2-naphthyl)-1*H*-1-indazolecarboxylate as a colorless oil. The compound was allowed to react with any of carboxylic acids and was then treated with an acid according to the procedure of Synthesis Process I-E. Each of the reaction mixtures was separated and purified by LC-MS under the conditions of Synthesis Process I-A, to give the following compounds.

EXAMPLE I-167

*N*1-{[3-(2-Naphthyl)-1*H*-5-indazolyl]methyl}-3-methoxypropanamide

MS (ESI)m/z 360 MH^+

EXAMPLE I-168

*N*1-{[3-(2-Naphthyl)-1*H*-5-indazolyl]methyl}-2-(3-thienyl)acetamide

MS (ESI)m/z 398 MH^+

The compound according to Examples I-169 to I-171 were synthesized by following Synthesis Process I-G.

Synthesis Process I-G

To an ice-cold solution of 373 mg of *tert*-butyl 5-(hydroxymethyl)-3-(2-naphthyl)-1*H*-1-indazolecarboxylate produced in Production Example I-33 in 10 ml dry tetrahydrofuran were added dropwise 0.17 ml of triethylamine and 0.09 ml of methanesulfonyl chloride, and the mixture was stirred for 20 minutes. Each 1 ml of the reaction mixture was pipetted into test tubes, each of which was treated with 0.4 ml of a 1 M solution of any of

amines in dimethylformamide with stirring for one day. The suspended reaction mixture was diluted with a small amount of water and was filtrated through a membrane filter. Each of the reaction mixtures was separated and purified by LC-MS under the conditions of Synthesis Process I-A and thereby yielded the following test compounds.

EXAMPLE I-169

4-{[3-(2-Naphthyl)-1*H*-5-indazolyl]methyl}morpholine

MS (ESI)m/z 344 MH^+

EXAMPLE I-170

5-(2,3-Dihydro-1*H*-1-indolylmethyl)-3-(2-naphthyl)-1*H*-indazole

MS (ESI)m/z 376 MH^+

EXAMPLE I-171

5-{[4-(2-Methoxyphenyl)piperazino]methyl}-3-(2-naphthyl)-1*H*-indazole

MS (ESI)m/z 449 MH^+

The compound according to Examples I-172 and I-173 were synthetically prepared by following Synthesis Process I-H.

Synthesis Process I-H

Into test tubes were pipetted 15 mg of *tert*-butyl 5-(hydroxymethyl)-3-(2-naphthyl)-1*H*-1-indazolecarboxylate produced in Production Example I-33 and 0.5 ml of tetrahydrofuran, each of which was treated with 1 equivalent of any of phenols. Each of the mixtures was

further treated with 15 mg of triphenylphosphine and 0.02 ml of a 40% solution of diethyl azodicarboxylate in toluene by standing still for one week. Each of the reaction mixtures was separated and purified by LC-MS under the conditions of Synthesis Process I-A, the solvent was removed by blowing nitrogen gas, and the residue was treated with 1 ml of a 1:1 mixture solution of trifluoroacetic acid and dichloromethane containing 10% triethylsilane by standing still for 1 hour. The solvent in the reaction mixture was removed by blowing nitrogen gas, the resulting residue was dissolved in 0.5 ml of N,N-dimethylformamide, was separated and purified by LC-MS under the conditions of Synthesis Process I-A and thereby yielded the following compounds.

EXAMPLE I-172

5-[(3-Methoxyphenoxy)methyl]-3-(2-naphthyl)-1*H*-indazole

MS (ESI)m/z 381 MH^+

EXAMPLE I-173

7-[3-(2-Naphthyl)-1*H*-5-indazolyl]methoxy-2*H*-2-chromenone

MS (ESI)m/z 419 MH^+

PRODUCTION EXAMPLE II-1-a

1-Bromo-4-fluoro-2-methoxy-benzene

A total of 10 g of 2-bromo-5-fluoro-phenol was dissolved in 105 ml of N,N-dimethylformamide, 10.9 g of potassium carbonate and 4.9 ml of iodomethane were added under ice-cooling, and the mixture was stirred at room

temperature for 3 hours. Water was added to the reaction mixture, followed by extracting with diethyl ether. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated, to give 9.75 g of the title compound as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, s), 6.59 (1H, td, J = 8.4, 2.8 Hz), 6.65 (1H, dd, J = 10.4, 2.8 Hz), 7.47 (1H, dd, J = 8.4, 6.0 Hz)

PRODUCTION EXAMPLE II-1-b

(5-Bromo-2-fluoro-4-methoxy-phenyl)-(3-fluoro-phenyl)-methanone

A total of 716 mg of aluminium chloride was suspended in 24.4 ml of dichloromethane and was then mixed with 0.65 ml of 3-fluorobenzoyl chloride and 1 g of 1-bromo-4-fluoro-2-methoxy-benzene obtained in Production Example II-1-a under stirring at -60°C. The mixture was raised in temperature to room temperature over 2.5 hours and was stirred for further 3 hours. Water was added to the reaction mixture under ice-cooling, followed by extracting with diethyl ether. The resulting organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:10), to give 856 mg of the title compound as white crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.98 (3H, s), 6.69 (1H, d, J = 11.6 Hz), 7.27 - 7.58 (4H, m), 7.83 (1H, d, J = 7.2 Hz)

PRODUCTION EXAMPLE II-1-c

4-Fluoro-5-(3-fluoro-benzoyl)-2-methoxy-benzonitrile

A total of 856 mg of (5-bromo-2-fluoro-4-methoxy-phenyl)-(3-fluoro-phenyl)-methanone obtained in Production Example II-1-b was dissolved in 13.1 ml of N,N-dimethylformamide, 185 mg of zinc cyanide, 13.6 mg of tris(dibenzylideneacetone)dipalladium and 17.4 mg of 1,1'-bis(diphenylphosphino)ferrocene were added thereto, and the mixture was stirred at 120°C in an atmosphere of nitrogen gas for 7 hours. After cooling to room temperature, water was added to the reaction mixture and the mixture was extracted with diethyl ether. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:2), to give 203 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.03 (3H, s), 6.78 (1H, d, J = 11.6 Hz), 7.30 - 7.37 (1H, m), 7.42 - 7.56 (3H, m), 7.89 (1H, d, J = 7.6 Hz)

PRODUCTION EXAMPLE II-1-d

3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazole-5-carbonitrile

A total of 203 mg of 4-fluoro-5-(3-fluoro-benzoyl)-2-methoxy-benzonitrile obtained in Production Example II-1-c

was dissolved in 3 ml of tetrahydrofuran and 3 ml of methanol, 7.4 ml of hydrazine monohydrate was added at room temperature under stirring, and the mixture was stirred at room temperature for 14 hours. Then, water was added and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with 1 N hydrochloric acid, saturated aqueous sodium hydrogencarbonate solution and brine, dried over magnesium sulfate and the solvent was evaporated. The resulting crystals were washed with diethyl ether, to give 172 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, CD_3OD) δ 4.01 (3H, s), 7.14 (1H, s), 7.18 (1H, td, J = 8.4, 2.8 Hz), 7.54 (1H, td, J = 8.4, 6.0 Hz), 7.62 - 7.68 (1H, m), 7.76 (1H, J = 8.4 Hz), 8.37 (1H, s)

PRODUCTION EXAMPLE II-1-e

3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazole-5-carboxylic acid

A total of 172 mg of 3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazole-5-carbonitrile obtained in Production Example II-1-d was dissolved in 2 ml of acetic acid, 0.7 ml of water and 0.5 ml of sulfuric acid, followed by stirring at 110°C for 18 hours. After cooling to room temperature, water was added to the reaction mixture. The resulting crystals were washed with water, to give 159 mg of the title compound as light pink crystals.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.99 (3H, s), 7.12 (1H, s), 7.14 - 7.20 (1H, m), 7.55 (1H, td, J = 8.0, 6.0 Hz), 7.61 - 7.67 (1H, m),

7.76 (1H, d, J = 8.0 Hz), 8.53 (1H, s)

PRODUCTION EXAMPLE II-2-a

(3-Bromo-6-fluoro-2-methoxy-phenyl)-(3-fluoro-phenyl)-methanol

A total of 1.64 ml of diisopropylamine was dissolved in 27 ml of tetrahydrofuran, 6.8 ml of a 1.57 M solution of n-butyllithium in hexane was added at -50°C under stirring, and the mixture was stirred at -30°C for 30 minutes. After cooling to -60°C, 2 g of 1-bromo-4-fluoro-2-methoxy-benzene obtained in Production Example II-1-a was added and the mixture was stirred at -60°C for 1 hour. Then, 1.55 ml of 3-fluoro-benzaldehyde was added, followed by stirring for 1 hour. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated, to give 2.4 g of the title compound as a yellow-brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.52 (3H, s), 3.56 (1H, d, J = 10.4 Hz), 6.16 (1H, d, J = 11.6 Hz), 6.86 (1H, t, J = 8.8 Hz), 6.92 - 6.99 (1H, m), 7.07 - 7.16 (2H, m), 7.30 (1H, td, J = 8.0, 6.0 Hz), 7.51 (1H, dd, J = 8.8, 6.0 Hz)

PRODUCTION EXAMPLE II-2-b

(3-Bromol-6-fluoro-2-methoxy-phenyl)-(3-fluoro-phenyl)-methanone

A total of 2.4 g of (3-bromo-6-fluoro-2-methoxy-

phenyl)-(3-fluoro-phenyl)-methanol obtained in Production Example II-2-a was dissolved in 24.3 ml of dichloromethane. Under ice-cooling and stirring, 1.28 g of 1-methylmorpholine-N-oxide, 3.65 g of powdery 4A molecular sieve and 128 mg of tetrapropylammonium perruthenate were added, followed by stirring at room temperature for 3 hours. Isopropyl alcohol was added to the reaction mixture and then the mixture was filtered through Celite. The resulting filtrate was evaporated, and the residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:8), to give 2.07 g of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s), 6.86 (1H, dd, J = 8.8, 8.0 Hz), 7.29 - 7.36 (1H, m), 7.42 - 7.50 (1H, m), 7.54 - 7.61 (2H, m), 7.66 (1H, dd, J = 8.8, 5.6 Hz)

PRODUCTION EXAMPLE II-2-c

5-Bromo-3-(3-fluoro-phenyl)-4-methoxy-1*H*-indazole

A total of 0.703 g of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-1-d, except using 0.959 g of (3-bromo1-6-fluoro-2-methoxy-phenyl)-(3-fluoro-phenyl)-methanone obtained in Production Example II-2-b.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.51 (3H, s), 7.10 - 7.17 (1H, m), 7.17 (1H, d, J = 8.8 Hz), 7.45 (1H, td, J = 8.0, 6.0 Hz), 7.56 (1H, d, J = 8.8 Hz), 7.69 - 7.75 (1H, m), 7.77 (1H, d, J = 8.0 Hz)

PRODUCTION EXAMPLE II-2-d

3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazole-5-carboxylic acid

A total of 230 mg of 5-bromo-3-(3-fluoro-phenyl)-4-methoxy-1*H*-indazole obtained in Production Example II-2-c was dissolved in 4.78 ml of tetrahydrofuran, and 0.99 ml of a 1.59 M solution of n-butyllithium in hexane was added under stirring at -78°C. After stirring at -78°C for 30 minutes, dry ice was added. After stirring at the same temperature for 10 minutes, saturated aqueous ammonium chloride solution was added. The mixture was extracted with ethyl acetate, and the resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:1), to give 41.1 mg of the title compound.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.55 (3H, s), 7.14 - 7.21 (1H, m), 7.36 (1H, d, J = 8.8 Hz), 7.50 (1H, td, J = 8.0, 6.0 Hz), 7.60 - 7.65 (1H, m), 7.72 (1H, d, J = 8.0 Hz), 7.88 (1H, d, J = 8.8 Hz)

PRODUCTION EXAMPLE II-3-a

2,4-Difluoro-3-[(3-fluoro-phenyl)-hydroxymethyl]-benzonitrile

A total of 9.35 g of the title compound was obtained as a yellow oil by the procedure of Production Example II-2-a, except from 5 g of 2,4-difluoro-benzonitrile.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.30 (1H, s), 6.98 - 7.18 (4H, m), 7.33 (1H, td, J = 8.0, 6.0 Hz), 7.58 - 7.65 (1H,m)

PRODUCTION EXAMPLE II-3-b

2,4-Difluoro-3-(3-fluoro-benzoyl)-benzonitrile

A total of 6.29 g of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-2-b, except from 9.35 g of 2,4-difluoro-3-{(3-fluoro-phenyl)-hydroxymethyl}-benzonitrile obtained in Production Example II-3-a.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.19 (1H, t, J = 8.0 Hz), 7.36 - 7.44 (1H, m), 7.52 (1H, td, J = 8.0, 6.0 Hz), 7.55 - 7.60 (2H, m), 7.78 - 7.86 (1H, m)

PRODUCTION EXAMPLE II-3-c

4-Fluoro-3-{(3-fluoro-phenyl)-1*H*-indazole-5-carbonitrile

A total of 479 mg of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-1-d, except from 952 mg of 2,4-difluoro-3-{(3-fluoro-benzoyl)-benzonitrile obtained in Production Example II-3-b.

^{1}H-NMR (400 MHz, CD_3OD) δ 7.17 - 7.23 (1H, m), 7.49 - 7.66 (4H, m), 7.70 - 7.75 (1H, m)

PRODUCTION EXAMPLE II-3-d

4-Fluoro-3-{(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid

A total of 246 mg of the title compound was obtained as pale gray crystals by the procedure of Production Example II-1-e, except from 220 mg of 4-fluoro-3-{(3-fluoro-phenyl)-1*H*-indazole-5-carbonitrile obtained in Production Example II-3-c.

^{1}H-NMR (400 MHz, CD_3OD) δ 7.14 - 7.21(1H, m), 7.39 (1H, d, J = 8.8 Hz), 7.51 (1H, td, J = 8.0, 6.0 Hz), 7.57 - 7.64 (1H, m), 7.68 - 7.73 (1H, m), 7.96 (1H, dd, J = 8.8, 6.4 Hz)

PRODUCTION EXAMPLE II-4-a

(5-Bromo-2-fluoro-4-methyl-phenyl)-(3-fluoro-phenyl)-methanol

A total of 11.6 g of the title compound was obtained as a pale yellow oil by the procedure of Production Example II-2-a, except from 5.98 g of 2-bromo-5-fluoro-toluene.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 6.06 (1H, s), 6.93 (1H, d, J = 11.2 Hz), 6.96 - 7.00 (1H, m), 7.08 - 7.18 (1H, m), 7.31 (1H, td, J = 8.0, 6.0 Hz), 7.63 (1H, d, J = 7.2 Hz)

PRODUCTION EXAMPLE II-4-b

(5-Bromol-2-fluoro-4-methyl-phenyl)-(3-fluoro-phenyl)-methanone

A total of 6.63 g of the title compound was obtained as a yellow oil by the procedure of Production Example II-2-b, except from 11.6 g of (5-bromo-2-fluoro-4-methyl-phenyl)-(3-fluoro-phenyl)-methanol obtained in Production Example II-4-a.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.48 (3H, s), 7.08 (1H, d, J = 10.4 Hz), 7.28 - 7.35 (1H, m), 7.46 (1H, td, J = 8.0, 5.6 Hz), 7.49 - 7.60 (2H, m), 7.73 (1H, d, J = 6.4 Hz)

PRODUCTION EXAMPLE II-4-c

5-Bromo-3-(3-fluoro-phenyl)-6-methyl-1*H*-indazole

A total of 1.57 g of the title compound was obtained

as white crystals by the procedure of Production Example II-1-d, except from 2.42 g of (5-bromol-2-fluoro-4-methyl-phenyl)-(3-fluoro-phenyl)-methanone obtained in Production Example II-4-b.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.56 3H, s), 7.09 - 7.16 (1H, m), 7.40 (1H, s), 7.49 (1H, td, J = 8.0, 6.0 Hz), 7.62 - 7.68 (1H, m), 7.70 - 7.75 (1H, m), 8.21 (1H, s), 10.10 (1H, brs)

PRODUCTION EXAMPLE II-4-d

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid

A total of 195 mg of the title compound was obtained as pale brown crystals by the procedure of Production Example II-2-d, except from 670 mg of 5-bromo-3-(3-fluoro-phenyl)-6-methyl-1*H*-indazole obtained in Production Example II-4-c.

^{1}H-NMR (400 MHz, CD_3OD) δ 2.71 (3H, s), 7.12 - 7.20 (1H, m), 7.41 (1H, s), 7.50 - 7.81 (4H, m), 8.61 (1H, s)

PRODUCTION EXAMPLE II-5-a

1,5-Dibromo-2,4-difluorobenzene

A total of 1.6 g of 1-bromo-2,4-difluorobenzene was suspended in 8.29 ml of sulfuric acid, and 1.62 g of N-bromosuccinimide was added under ice-cooling. After stirring at room temperature for 17 hours, the reaction mixture was poured onto ice-water and extracted with ethyl acetate. The resulting organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over magnesium sulfate and the solvent was

evaporated. The residue was purified and separated by silica gel column chromatography (hexane), to give 2.18 g of the title compound as a pale yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ 6.99 (1H, t, J = 8.0 Hz), 7.77 (1H, t, J = 6.8 Hz)

PRODUCTION EXAMPLE II-5-b

(5-Bromo-2,4-difluoro-phenyl)-(3-fluoro-phenyl)-methanol

A total of 2.02 g of 1,5-dibromo-2,4-difluorobenzene obtained in Production Example II-5-a was dissolved in 38 ml of diethyl ether, and 4.9 ml of a 1.58 M solution of n-butyllithium in hexane was added under stirring at -70°C. After stirring for 1 hour, 4.9 ml of m-fluorobenzaldehyde was added and the mixture was stirred for 15 minutes. Saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extracting with ethyl acetate. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:10), to give 0.96 g of the title compound.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.07 (1H, d, J = 3.2 Hz), 6.87 (1H, dd, J = 9.6, 8.4 Hz), 6.95 - 7.04 (1H, m), 7.07 - 7.18 (2H, m), 7.33 (1H, td, J = 8.4, 6.0 Hz), 7.73 (1H, t, J = 8.0 Hz)

PRODUCTION EXAMPLE II-5-c

(5-Bromo-2,4-difluoro-phenyl)-(3-fluoro-phenyl)-methanone

A total of 8.34 g of the title compound was obtained

by the procedure of Production Example II-2-b, except from 17.0 g of (5-bromo-2,4-difluoro-phenyl)-(3-fluoro-phenyl)-methanol obtained in Production Example II-5-b.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.02 (1H, t, J = 8.4 Hz), 7.30 - 7.64 (4H, m), 7.82 (1H, t, J = 7.6 Hz)

PRODUCTION EXAMPLE II-5-d

2,4-Difluoro-5-(3-fluoro-benzoyl)-benzonitrile

A total of 1.63 g of the title compound was obtained as yellow-brown crystals by the procedure of Production Example II-1-c, except from 4.03 g of (5-bromo-2,4-difluoro-phenyl)-(3-fluoro-phenyl-methanone obtained in Production Example II-5-c.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.13 (1H, t, J = 8.8 Hz), 7.34 - 7.56 (4H, m), 7.93 (1H, t, J = 7.2 Hz)

PRODUCTION EXAMPLE II-5-e

6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carbonitrile

A total of 0.982 g of the title compound was obtained as pale yellow crystals by the procedure of Production Example I-1-d, except from 1.63 g of 2,4-difluoro-5-(3-fluoro-benzoyl)-benzonitrile obtained in Production Example II-5-d.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.26 - 7.36 (1H, m), 7.50 - 7.63 (1H, m), 7.73 (1H, d, J = 10.0 Hz), 7.80 - 7.86 (1H, m), 7.91 (1H, d, J = 8.0 Hz), 8.88 (1H, d, J = 6.0Hz)

PRODUCTION EXAMPLE II-5-f

6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid

A total of 415 mg of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-1-e, except from 653 mg of 6-fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carbonitrile obtained in Production Example II-5-e.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.27 - 7.35 (1H, m), 7.49 (1H, d, J = 11.2 Hz), 7.63 (1H, td, J = 8.0, 6.0 Hz), 7.70 - 7.76 (1H, m), 7.82 (1H, d, J = 8.0 Hz)

PRODUCTION EXAMPLE II-6

<u>3-(3-Fluoro-phenyl)-6-hydroxy-1*H*-indazole-5-carboxylic acid</u>

A total of 96.2 mg of 3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazole-5-carboxylic acid obtained in Production Example II-1-e was dissolved in 3.36 ml of dichloromethane, 4.0 ml of a 1.0 M solution of boron tribormide in dichloromethane was added under ice-cooling, and the mixture was stirred at room temperature for 1.5 hours. Water was added to the reaction mixture, followed by extracting with ethyl acetate. The resulting organic layer was washed brine, dried over magnesium sulfate and the solvent was evaporated, to give 84.1 mg of the crude product of the title compound.

^{1}H-NMR (400 MHz, CD_3OD) δ 6.93 (1H, s), 7.13 - 7.23 (1H, m), 7.50 - 7.79 (3H, m), 8.63 (1H, s)

PRODUCTION EXAMPLE II-7-a

<u>2-Amino-4-fluoro-benzoic acid ethyl ester</u>

A total of 10 g of 2-amino-4-fluoro-benzoic acid was

240

dissolved in 129 ml of ethanol, 6.45 ml of sulfuric acid was added and the mixture was heated under reflux for 11 hours. After cooling to room temperature, the solvent was evaporated to about half. Water was added and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:5), to give 7.57 g of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, J = 6.8 Hz), 4.32 (2H, q, J = 6.8 Hz), 5.88 (2H, brs), 6.28 - 6.38 (2H, m), 7.88 (1H, dd, J = 8.8, 6.8 Hz)

PRODUCTION EXAMPLE II-7-b

2-Acetylamino-4-fluoro-benzoic acid ethyl ester

A total of 3.84 g of 2-amino-4-fluoro-benzoic acid ethyl ester obtained in Production Example II-7-a was dissolved in 50 ml of pyridine, 1.64 ml of acetyl chloride was added under ice-cooling, and the mixture was stirred for 1 hours. The reaction mixture was diluted with water and was extracted with diethyl ether. The resulting organic layer was washed with 1 N hydrochloric acid and brine, dried over magnesium sulfate, and then evaporated, to give 4.0 g of the title compound.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, t, J = 6.8 Hz), 2.14 (3H, s),

4.38 (2H, q, J = 6.8 Hz), 6.73 - 6.81 (1H, m), 8.06 (1H, dd, J = 8.8, 6.4 Hz), 8.53 (1H, dd, J = 12.0, 2.4 Hz), 11.3 (1H, brs)

PRODUCTION EXAMPLE II-7-c

2-Acetylamino-4-fluoro-5-iodo-benzoic acid ethyl ester

A total of 3.12 g of silver sulfate was suspended in 45 ml of sulfuric acid, 5 ml of water was added, and the mixture was stirred at room temperature for 15 minutes. 1 ml of iodine monochloride was added, followed by stirring at room temperature for 1 hour. The mixture was filtered, and to 44 ml of the filtrate was added 2 g of 2-acetylamino-4-fluoro-benzoic acid ethyl ester obtained in Production Example II-7-b under ice-cooling, and the mixture was stirred for 1 hour. The reaction mixture was poured onto ice-water and was extracted with ethyl acetate. The resulting organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:5), to give 2.9 g of the title compound as white crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, t, J = 6.8 Hz), 2.24 (3H, s), 4.39 (2H, q, J = 6.8 Hz), 8.41 (1H, d, J = 7.2 Hz), 8.59 (1H, d, J = 11.2 Hz)

PRODUCTION EXAMPLE II-7-d

2-Acetylamino-4-fluoro-5-(3-fluoro-benzoyl)-benzoic acid ethyl ester

A total of 812 mg of 2-acetylamino-4-fluoro-5-iodo-benzoic acid ethyl ester obtained in Production Example II-7-c was dissolved in 13.9 ml of anisole, and 956 mg of potassium carbonate, 356 mg of 3-fluorophenyl-boronic acid and 49 mg of bis(triphenylphosphine)palladium dichloride were added. After replacing the inside atmosphere of the reaction system with carbon monoxide gas, the mixture was stirred at 80°C in an atmosphere of carbon monoxide (normal pressure) for 14 hours. After cooling to room temperature and replacing the inside atmosphere of the reaction system with nitrogen gas, water was added and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:5), to give 234 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, t, J = 6.8 Hz), 2.27 (3H, s), 4.41 (2H, q, J = 6.8 Hz), 7.05 - 7.12 (1H, m), 7.20 - 7.46 (3H, m), 8.15 (1H, d, J = 8.8 Hz), 8.64 (1H, d, J = 13.6 Hz)

PRODUCTION EXAMPLE II-7-e

6-Acetylamino-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid ethyl ester

A total of 160 mg of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-1-d, except from 234 mg of 2-acetylamino-4-

fluoro-5-(3-fluoro-benzoyl)-benzoic acid ethyl ester obtained in Production Example II-7-d.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.47 (3H, t, J = 6.8 Hz), 2.32 (3H, s), 4.46 (2H, q, J = 6.8 Hz), 7.12 - 7.19 (1H, m), 7.51 (1H, td, J = 8.0, 6.0 Hz), 7.64 - 7.70 (1H, m), 7.75 (1H, d, J = 8.0 Hz), 8.79 (1H, s), 8.99 (1H, s)

PRODUCTION EXAMPLE II-7-f

6-Acetylamino-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid

A total of 160 mg of 6-acetylamino-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid ethyl ester obtained in Production Example II-7-e was dissolved in 3 ml of ethanol and 1 ml of 5 N aqueous sodium hydroxide solution, and the solution was stirred at 50°C for 2 hours. After cooling to room temperature, 1 N hydrochloric acid was added and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated, to give 155 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, CD_3OD) δ 2.24 (3H, s), 7.14 - 7.21 (1H, m), 7.56 (1H, td, J = 8.0, 6.0 Hz), 7.63 - 7.68 (1H, m), 7.77 (1H, d, J = 8.0 Hz), 8.79 - 8.85 (2H, m)

PRODUCTION EXAMPLE II-8-a

4-Fluoro-3-[(3-fluorophenyl)-hydroxymethyl]-5-methoxybenzonitrile

To a solution of 15.0 g of 4-fluoro-3-

methoxybenzonitrile and 21.8 ml of N,N,N',N',N"-pentamethyldiethylenetriamine in 300 ml tetrahydrofuran was added 65.5 ml of a 1.59 M solution of n-butyllithium in hexane at -78°C in an atmosphere of nitrogen gas, followed by stirring at the same temperature for 1 hour. At the same temperature, 10.5 ml of 3-fluorobenzaldehyde was added dropwise, followed by stirring at the same temperature for 1 hour. Then, water was added and the mixture was extracted with diethyl ether. The organic layer was washed with saturated aqueous ammonium chloride solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:n-hexane = 1:10 to 1:3), to give 7.1 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.55 (1H, br s), 3.89 (3H, s), 6.13 (1H, s), 6.98 (1H, dt, J = 2.0, 8.0 Hz), 7.10 (1H, d, J = 8.0 Hz), 7.12 (1H, dd, J = 2.0, 8.0 Hz), 7.16 (1H, d, J = 8.0 Hz), 7.31 (1H, dt, J = 5.6, 8.0 Hz), 7.50 (1H, dd, J = 2.0, 5.6 Hz)

PRODUCTION EXAMPLE II-8-b

4-Fluoro-3-(3-fluorobenzoyl)-5-methoxybenzonitrile

To a solution of 7.0 g of 4-fluoro-3-[(3-fluorophenyl)-hydroxymethyl]-5-methoxybenzonitrile in 70 ml toluene was added 11.1 g of activated manganese dioxide at room temperature. After stirring at 60°C for one day, the manganese dioxide was filtered off through Celite. The

solvent was removed and the crude product was purified and separated by silica gel column chromatography (ethyl acetate:n-hexane = 1:3), to give 640 mg of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.99 (3H, s), 7.35 (1H, dt, J = 1.2, 5.6 Hz), 7.37 (1H, dd, J = 2.0, 8.0 Hz), 7.42 (1H, dd, J = 2.0, 5.6 Hz), 7.48 (1H, dt, J = 5.6, 8.0 Hz), 7.51 - 7.58 (2H, m)

PRODUCTION EXAMPLE II-8-c

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carbonitrile

To a solution of 640 mg of 4-fluoro-3-(3-fluorobenzoyl)-5-methoxybenzonitrile in 6 ml ethanol was added 3 ml of hydrazine monohydrate at room temperature, followed by stirring at 70°C for one day. The reaction mixture was evaporated, and the resulting crystals were collected by filtration. The crystals were sequentially washed with ethanol and diethyl ether, to give 590 mg of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 4.03 (3H, s), 7.23 - 7.29 (1H, m), 7.25 (1H, d, J = 1.2 Hz), 7.55 (1H, dt, J = 6.4, 8.0 Hz), 7.78 (1H, ddd, J = 1.2, 2.4, 6.4 Hz), 7.88 (1H, dt, J = 1.2, 8.0 Hz), 8.31 (1H, d, J = 1.2 Hz)

PRODUCTION EXAMPLE II-8-d

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carboxylic acid

To 450 mg of 3-(3-fluorophenyl)-7-methoxy-1*H*-indazole-5-carbonitrile were sequentially added 6 ml of glacial acetic acid, 2 ml of water and 2 ml of concentrated

sulfuric acid, followed by stirring at 100°C for one day. After standing to cool, water was added to the reaction mixture and the resulting crystals were collected by filtration. The crystals were sequentially washed with isopropanol and diethyl ether, to give 428 mg of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 4.03 (3H, s), 7.27 (1H, dt, J = 2.4, 8.0 Hz), 7.37 (1H, s), 7.60 (1H, dt, J = 6.4, 8.0 Hz), 7.69 (1H, ddd, J = 1.2, 2.4, 6.4 Hz), 7.80 (1H, d, J = 8.0 Hz), 8.24 (1H, s)

PRODUCTION EXAMPLE II-9-a

(5-Bromo-2-fluoro-3-methylphenyl)-(3-fluorophenyl)methanol

In an atmosphere of nitrogen gas, 74.1 ml of a 1.57 M solution of n-butyllithium in hexane was added to a solution of 16.3 ml of *N,N*-diisopropylamine in 400 ml tetrahydrofuran at 0°C, and the mixture was stirred at the same temperature for 30 minutes. After cooling to -78°C, a solution of 20.0 g of 5-bromo-2-fluorotoluene in 40 ml tetrahydrofuran was added dropwise. After stirring at the same temperature for 1 hour, 11.2 ml of 3-fluorobenzaldehyde was added dropwise and the mixture was stirred at the same temperature for 3 hours. The reaction mixture was neutralized with 1 N hydrochloric acid and diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The crude product was purified and

separated by silica gel column chromatography (ethyl acetate:n-hexane = 1:20), to give 20.6 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.23 (3H, s), 2.34 (1H, d, J = 4.0 Hz), 6.06 (1H, d, J = 4.0 Hz), 6.98 (1H, dt, J = 2.4, 8.0 Hz), 7.12 (1H, d, J = 8.0 Hz), 7.17 (1H, d, J = 8.0 Hz), 7.25 (1H, d, J = 6.0 Hz), 7.31 (1H, dt, J = 6.0, 8.0 Hz), 7.50 (1H, dd, J = 2.4, 6.0 Hz)

PRODUCTION EXAMPLE II-9-b

5-Bromo-3-(3-fluorophenyl)-7-methyl-1*H*-indazole

To a solution of 20.0 g of (5-bromo-2-fluoro-3-methylphenyl)-(3-fluorophenyl)methanol in 200 ml toluene was added 16.7 g of activated manganese dioxide at room temperature. After stirring at 80°C for 2 hours, the manganese dioxide was filtered off through Celite. After removing the solvent by distillation, to a solution of the residue in 100 ml of ethanol was added 15.5 ml of hydrazine monohydrate at room temperature and the mixture was heated under reflux for one day. The reaction mixture was evaporated and diluted with ethyl acetate. The organic layer was sequentially washed with saturated aqueous ammonium chloride solution and brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. A solution of the residue in 20 ml pyridine was stirred in a sealed tube at 200°C for 10 hours. After cooling, the reaction mixture was evaporated, the residue was dissolved

in ethyl acetate and 5 N hydrochloric acid, and the aqueous layer was extracted with ethyl acetate. The collected organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The resulting crystals were washed with ethyl acetate, to give 11.3 g of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 2.58 (3H, s), 7.15 (1H, ddd, J = 0.8, 2.4, 8.0 Hz), 7.33 (1H, dd, J = 0.8, 1.6 Hz), 7.53 (1H, dt, J = 6.0, 8.0 Hz), 7.61 (1H, ddd, J = 1.6, 2.4, 6.0 Hz), 7.72 (1H, ddd, J = 0.8, 1.6, 8.0 Hz), 8.31 (1H, dd, J = 0.8, 1.6 Hz)

PRODUCTION EXAMPLE II-9-c

5-Bromo-3-(3-fluorophenyl)-7-methyl-1-trityl-1*H*-indazole

To a solution of 2.56 g of 5-bromo-3-(3-fluorophenyl)-7-methyl-1*H*-indazole in 30 ml of dimethylformamide was added 0.50 g of sodium hydride at room temperature, and the mixture was stirred at the same temperature for 15 minutes. At the same temperature, 2.34 g of triphenylmethane chloride was added and the mixture was stirred at the same temperature for one day. Water was added to the reaction mixture and the mixture was diluted with ethyl acetate. The organic layer was sequentially washed with saturated aqueous ammonium chloride solution and brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:n-hexane = 1:10) and the resulting crystals were washed with diethyl ether, to

give 1.94 g of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, s), 7.01 (1H, ddd, J = 0.8, 2.4, 8.0 Hz), 7.08 (1H, dd, J = 0.8, 1.6 Hz), 7.10 - 7.32 (15H, m), 7.37 (1H, dt, J = 6.0, 8.0 Hz), 7.41 (1H, ddd, J = 1.6, 2.4, 6.0 Hz), 7.54 (1H, ddd, J = 0.8, 1.6, 8.0 Hz), 8.07 (1H, dd, J = 0.8, 1.6 Hz)

PRODUCTION EXAMPLE II-9-d

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carbonitrile

To a solution of 1.5 g of 5-bromo-3-(3-fluorophenyl)-7-methyl-1-trityl-1*H*-indazole in 15 ml dimethylformamide were added 0.64 g of zinc cyanide and 0.32 g of tetrakis(triphenylphosphine)palladium(0) at room temperature, and the mixture was stirred at 100°C for one day. At the same temperature, 0.32 g of tetrakis(triphenylphosphine)palladium(0) was added and the mixture was stirred at 130°C for one day. The reaction mixture was diluted with ethyl acetate, and the organic layer was sequentially washed with saturated aqueous ammonium chloride solution and brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:n-hexane = 1:10 to 1:1) and the resulting crystals were washed with diethyl ether, to give 431 mg of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 2.57 (3H, s), 7.26 (1H, dd, J = 2.4,

8.0 Hz), 7.53 (1H, s), 7.56 (1H, dt, J = 6.0, 8.0 Hz), 7.79 (1H, dt, J = 2.4, 6.0 Hz), 7.89 (1H, d, J = 8.0 Hz), 8.55 (1H, s)

PRODUCTION EXAMPLE II-9-e

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carboxylic acid

To 430 mg of 3-(3-fluorophenyl)-7-methyl-1*H*-indazole-5-carbonitrile were sequentially added 6.0 ml of glacial acetic acid, 2.0 ml of water and 2.0 ml of concentrated sulfuric acid, followed by stirring at 100°C for one day. After standing to cool, the reaction mixture was diluted with 20 ml of water, and the resulting crystals were collected by filtration. The crystals were sequentially washed with water and diethyl ether, to give 360 mg of the title compound as colorless crystals.

^{1}H-NMR (400MHz, DMSO-D_6) δ 2.58 (3H, s), 7.27 (1H, dd, J = 2.4, 8.0 Hz), 7.61 (1H, q, J = 8.0 Hz), 7.71 (1H, dd, J = 2.4, 8.0 Hz), 7.76 (1H, s), 7.81 (1H, d, J = 8.0 Hz), 8.46 (1H, s)

PRODUCTION EXAMPLE II-10-a

(3-Bromo-6-fluoro-2-methoxy-phenyl)-naphthalen-2-yl-methanol

In an atmosphere of nitrogen gas, 2.38 ml of a 2.66 M solution of n-butyllithium in hexane was added to a solution of 0.64 g of *N,N*-diisopropylamine in 9 ml tetrahydrofuran at -78°C. After stirring at the same temperature for 1 hour, 1.18 g of 1-bromo-4-fluoro-2-methoxy-benzene obtained in Production Example II-1-a was

251

added dropwise. After stirring at the same temperature for 1 hour and 20 minutes, a solution of 0.99 g of 2-naphthoaldehyde in 4 ml tetrahydrofuran was added dropwise. After stirring at the same temperature for 1 hour and 20 minutes, water was added under ice-cooling and the mixture was extracted with diethyl ether for two times. The extract was sequentially washing with water and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography, to give 1.72 g of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.46 (3H, s), 3.68 (1H, d, J = 10.8 Hz), 6.35 (1H, d, J = 10.8 Hz), 6.88 (1H, t, J = 8.8 Hz), 7.42 - 7.53 (4H, m), 7.80 - 7.85 (4H, m)

PRODUCTION EXAMPLE II-10-b

(3-Bromo-6-fluoro-2-methoxy-phenyl)-naphthalen-2-yl-methanone

To a solution of 1.72 g of (3-bromo-6-fluoro-2-methoxy-phenyl)-naphthalen-2-yl-methanol in 34.4 ml methylene chloride was added 5.16 g of activated manganese dioxide, followed by stirring at room temperature for 17 hours. Then, the manganese dioxide was filtered off through Celite. The solvent was removed by distillation, to give 1.63 g of the title compound as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s), 6.91 (1H, dd, J = 8.0, 8.8 Hz), 7.51 - 7.55 (1H, m), 7.59 - 7.68 (2H, m), 7.87 - 7.93 (3H,

m), 8.02 (1H, dd, J = 1.6, 8.4 Hz), 8.20 (1H, bs)

PRODUCTION EXAMPLE II-10-c

5-Bromo-4-methoxy-3-naphthalen-2-yl-1*H*-indazole

A total of 1.63 g of (3-bromo-6-fluoro-2-methoxy-phenyl)-naphthalen-2-yl-methanone was dissolved in 15 ml of pyridine, 2.2 ml of hydrazine monohydrate was added, followed by stirring at 100°C for 6 hours. Water was added to the reaction mixture, and then it was extracted with ethyl acetate for two times. The organic layer was sequentially washed with 1 N hydrochloric acid, water, saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was removed by distillation. Then, the resulting crystals were washed with hexane once and dried in vacuo, to give 0.923 g of the title compound as brown crystals.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.39 (3H, s), 7.31 (1H, d, J = 8.8 Hz), 7.52 - 7.58 (3H, m), 7.91 - 8.03 (4H, m), 8.40 (1H, bs)

ESI-MS: m/z=351, 353 $(M-H)^-$

PRODUCTION EXAMPLE II-10-d

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid

In an atmosphere of nitrogen gas, 2.94 ml of a 2.66 M solution of *n*-butyllithium in hexane was added to a solution of 0.923 g of 5-bromo-4-methcxy-3-naphthalen-2-yl-1*H*-indazole in 26 ml tetrahydrofuran at -78°C. After stirring at the same temperature for 1 hour and 15 minutes, carbon dioxide gas was bubbled into the reaction mixture at

the same temperature for 10 minutes. After stirring at the same temperature for further 15 minutes, the mixture was stirred at room temperature for 20 minutes. Saturated aqueous ammonium chloride solution was added and the mixture was extracted ethyl acetate for two times. The organic layer was washed with brine once, dried over anhydrous magnesium sulfate and the solvent was evaporated. The resulting crystals were washed with one portion of a 1:1 solvent of hexane:diethyl ether, and dried in vacuo, to give 0.586 g of the title compound as brown crystals.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.48 (3H, s), 7.36 (1H, d, J = 8.8 Hz), 7.51 - 7.55 (2H, m), 7.88 - 8.02 (5H, m), 8.39 (1H, bs)

ESI-MS: m/z=317 $(M-H)^-$

PRODUCTION EXAMPLE II-11-a

3-Bromo-6-fluoro-2-methoxy-benzaldehyde

In an atmosphere of nitrogen gas, 18.7 ml of a 2.66 M solution of *n*-butyllithium in hexane was added to a solution of 5 g of *N,N*-diisopropylamine in 89 ml tetrahydrofuran at -78°C. After stirring at the same temperature for 1 hour and 10 minutes, 9.27 g of 1-bromo-4-fluoro-2-methoxy-benzene obtained in Production Example II-1-a was added dropwise. After stirring at the same temperature for 1.5 hours, 5.52 ml of N-formylpiperidine was added dropwise. After stirring at the same temperature for 25 minutes, 9 ml of acetic acid was added at the same temperature, water was added at room temperature, and the

mixture was extracted with diethyl ether for three times. The extract was sequentially washed with 0.2 N hydrochloric acid, water and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography, to give 5.65 g of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.97 (3H, s), 6.90 (1H, dd, J = 9.0, 9.6 Hz), 7.76 (1H, dd, J = 5.6, 9.0 Hz), 10.35 (1H, s)

PRODUCTION EXAMPLE II-11-b

Benzo[*b*]furan-2-yl-(3-bromo-6-fluoro-2-methoxy-phenyl)-methanol

In an atmosphere of nitrogen gas, 3.56 ml of a 2.66 M solution of n-butyllithium in hexane was added to a solution of 1.12 g of 2,3-benzofuran in 10 ml tetrahydrofuran at -78°C. After stirring at the same temperature for 10 minutes, the mixture was stirred under ice-cooling for 15 minutes and was then stirred at -78°C for 8 minutes. Then, a solution of 2 g of 3-bromo-6-fluoro-2-methoxy-benzaldehyde in 3.5 ml tetrahydrofuran was added dropwise at the same temperature. After stirring at the same temperature for 30 minutes, saturated aqueous ammonium chloride solution was added at the same temperature. Water was added at room temperature and the mixture was extracted with diethyl ether for two times. The organic layer was sequentially washed with water and

brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography, to give 2 g of the title compound as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.74 - 3.78 (4H, m), 6.28 (1H, d, J = 10.4 Hz), 6.647-6.652 (1H, m), 6.86 (1H, t, J = 9.2 Hz), 7.18 - 7.26 (2H, m), 7.40 - 7.43 (1H, m), 7.51 - 7.54 (2H, m)

PRODUCTION EXAMPLE II-11-c

Benzo[*b*]furan-2-yl-(3-bromo-6-fluoro-2-methoxy-phenyl)-methanone

A total of 1.93 g of the title compound was obtained as a yellow oil by the procedure of Production Example II-10-b, except from 2 g of benzo[*b*]furan-2-yl-(3-bromo-6-fluoro-2-methoxy-phenyl)-methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.86 (3H, s), 6.90 (1H, dd, J = 8.0, 8.8 Hz), 7.29 - 7.33 (1H, m), 7.37 (1H, bs), 7.48 - 7.53 (1H, m), 7.58 - 7.61 (1H, m), 7.64 - 7.69 (2H, m)

PRODUCTION EXAMPLE II-11-d

3-Benzo[*b*]furan-2-yl-5-bromo-4-methoxy-1*H*-indazole

A total of 1.38 g of the title compound was obtained as brown crystals by the procedure of Production Example II-10-c, except from 1.93 g of benzo[*b*]furan-2-yl-(3-bromo-6-fluoro-2-methoxy-phenyl)-methanone.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.86 (3H, s), 7.25 - 7.37 (3H, m), 7.53 (1H, d, J = 1.2 Hz), 7.57 - 7.61 (2H, m), 7.69 - 7.71 (1H,

m)

ESI-MS: m/z=341, 343 $(M-H)^-$

PRODUCTION EXAMPLE II-11-e

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid

A total of 0.2 g of the title compound was obtained as brown crystals by the procedure of Production Example II-10-d, except from 0.69 g of 3-benzo[*b*]furan-2-yl-5-bromo-4-methoxy-1*H*-indazole.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.48 (3H, s), 7.36 (1H, d, J = 8.8 Hz), 7.51 - 7.55 (2H, m), 7.88 - 8.02 (5H, m), 8.39 (1H, bs)

ESI-MS: m/z=307 (M-H).

PRODUCTION EXAMPLE II-12-a

Benzo[*b*]thiophen-2-yl-(3-bromo-6-fluoro-2-methoxy-phenyl)-methanol

A total of 2.14 g of the title compound was obtained as an orange oil by the procedure of Production Example II-11-b, except from 2 g of 3-bromo-6-fluoro-2-methoxy-benzaldehyde obtained in Production Example II-11-a and benzo[*b*]thiophene.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.66 (3H, s), 4.05 (1H, d, J = 11.2 Hz), 6.38 (1H, d, J = 11.2 Hz), 6.88 (1H, t, J = 9.2 Hz), 6.97 - 6.98 (1H, m), 7.26 - 7.33 (2H, m), 7.54 (1H, dd, J = 6.0, 8.8 Hz), 7.64 - 7.66 (1H, m), 7.77 - 7.79 (1H, m)

PRODUCTION EXAMPLE II-12-b

Benzo[*b*]thiophen-2-yl-(3-bromo-6-fluoro-2-methoxy-phenyl)-

methanone

A total of 2.04 g of the title compound was obtained as an orange oil by the procedure of Production Example II-10-b, except from 2.14 g of benzo[*b*]thiophen-2-yl-(3-bromo-6-fluoro-2-methoxy-phenyl)-methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (3H, s), 6.91 (1H, dd, J = 7.6, 8.8 Hz), 7.37 - 7.41 (1H, m), 7.46 - 7.50 (1H, m), 7.64 - 7.68 (2H, m), 7.81 - 7.84 (1H, m), 7.88 - 7.90 (1H, m)

PRODUCTION EXAMPLE II-12-c

3-Benzo[*b*]thiophen-2-yl-5-bromo-4-methoxy-1*H*-indazole

A total of 1.42 g of the title compound was obtained as black-green crystals by the procedure of Production Example II-10-c, except from 2.04 g of benzo[*b*]thiophen-2-yl-(3-bromo-6-fluoro-2-methoxy-phenyl)-methanone.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.76 (3H, s), 7.29 (1H, d, J = 8.8 Hz), 7.33 - 7.39 (2H, m), 7.58 (1H, d, J = 8.8 Hz), 7.86 - 7.88 (2H, m), 8.10 (1H, bs)

ESI-MS: m/z=357, 359 $(M-H)^-$

PRODUCTION EXAMPLE II-12-d

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid

A total of 0.64 g of the title compound was obtained as black-green crystals by the procedure of Production Example II-10-d, except from 1.42 g of 3-benzo[*b*]thiophen-2-yl-5-bromo-4-methoxy-1*H*-indazole.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.84 (3H, s), 7.33 - 7.39 (3H, m), 7.86

- 7.90 (3H, m), 8.14 (1H, bs)

ESI-MS: m/z=323 $(M-H)^-$

PRODUCTION EXAMPLE II-13-a

2,4-Difluoro-3-formyl-benzonitrile

In an atmosphere of nitrogen gas, 66 ml of a 1.6 M solution of n-butyllithium in hexane was added to an ice-cold solution of 11.1 g of *N,N*-diisopropylamine in 100 ml tetrahydrofuran, and the mixture was stirred at the same temperature for 20 minutes. After cooling to -78°C, a solution of 13.9 g of 2,4-difluorobenzonitrile in 15 ml tetrahydrofuran was added dropwise. After stirring at the same temperature for 10 minutes, 8.6 ml of dimethylformamide was added dropwise and the mixture was stirred at the same temperature for 15 minutes. After adding 20 ml of glacial acetic acid to the reaction mixture, 200 ml of water was added and the mixture was extracted with diethyl ether for two times. The organic layer was sequentially washed with 0.2 N hydrochloric acid and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The resulting crude crystals were triturated with diethyl ether-n-hexane, to give 8.61 g of the title compound as bright yellow crystals.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.53 (1H, t, J=8.8Hz), 8.33(1H, ddd, J=6.0,7.2,8.8Hz), 10.17 (1H, s)

PRODUCTION EXAMPLE II-13-b

4-Fluoro-1*H*-indazole-5-carbonitrile

259

A total of 8.55 g of 2,4-diflucro-3-formyl-benzonitrile obtained in Production Example II-13-a was dissolved in 40 ml of tetrahydrofuran and 40 ml of methanol, and 5.1 ml of hydrazine monohydrate was added, followed by stirring at room temperature for three days and was further stirred at 50°C for 3 hours and at 70°C for 3 hours. The reaction mixture was added with 150 ml of ice-water, 300 ml of ethyl acetate and 100 ml of tetrahydrofuran were added, and unnecessary matters were filtered off. The organic layer was sequentially washed with water and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 1:9 to 1:4), to give 509 mg of the title compound as bright yellow crystals. In addition, a portion with impurities was purified again by silica gel column chromatography (ethyl acetate:n-hexane = 1:4 to 1:0), to give 1.80 g of the title compound as bright yellow crystals.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.58 (1H, d, J = 8.8 Hz), 7.70 (1H, dd, J = 6.0, 8.8 Hz), 8.45 (1H, s), 13.94 (1H, s)

PRODUCTION EXAMPLE II-13-c

4-Fluoro-1*H*-indazole-5-carboxylic acid methyl ester

To 1.65 g of 4-fluoro-1*H*-indazole-5-carbonitrile obtained in Production Example II-13-b were added 8 ml of glacial acetic acid, 8 ml of water and 16 ml of concentrated sulfuric acid, and the mixture was stirred at

110°C for 4 hours. After standing to cool, 150 mg of ice-water was added, and the precipitated carboxylic acid was collected by filtration. Under ice-cooling, to a solution of the resulting carboxylic acid in 12 ml dimethylformamide and 40 ml tetrahydrofuran was added an excess amount of a solution of diazomethane in diethyl ether, and the mixture was stirred at the same temperature for 45 minutes. The solvent was evaporated, and the residue was dissolved in 100 ml of ethyl acetate. The mixture was sequentially washed with saturated aqueous sodium hydrogencarbonate solution, water and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 1.98 g of the title compound as bright yellow crystals.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.87 (3H, s), 7.45 (1H, d, J = 8.8 Hz), 7.82 (1H, dd, J = 6.8, 8.8 Hz), 8.36 (1H, s), 13.70 (1H, s)

PRODUCTION EXAMPLE II-13-d

3-Bromo-4-fluoro-1*H*-5-indazolecarboxylic acid methyl ester

To a solution of 2.2 g of 4-fluoro-1*H*-5-indazolecarboxylic acid methyl ester obtained in Production Example II-13-c in 20 ml dimethylformamide was added 2.12 g of N-bromosuccinimide at room temperature, and the mixture was stirred at the same temperature for 1 hour. After removing the solvent by distillation, 120 ml of ethyl acetate was added to the residue. The mixture was sequentially washed with half-saturated aqueous sodium hydrogencarbonate solution, water and brine, dried over

anhydrous magnesium sulfate and the solvent was evaporated, to give 3.0 g of the title compound as bright yellow crystals.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.88 (3H, s), 7.48 (1H, d, J = 8.8 Hz), 7.85 (1H, dd, J = 6.4, 8.8 Hz), 14.00 (1H, s)

PRODUCTION EXAMPLE II-13-e

3-Bromo-4-fluoro-1-trityl-1*H*-indazole-5-carboxylic acid methyl ester

Under ice-cooling, to a solution of 2.99 g of 3-bromo-4-fluoro-1*H*-5-indazolecarboxylic acid methyl ester obtained in Production Example II-13-d in 30 ml tetrahydrofuran was added 526 mg of 60% sodium hydride, and the mixture was stirred for 25 minutes. Then, 3.21 g of triphenylmethyl chloride was added and the mixture was stirred at the same temperature for 15 minutes and further stirred at room temperature for 45 minutes. The reaction mixture was ice-cooled again, saturated aqueous sodium hydrogencarbonate solution was added and the mixture was extracted with 100 ml of ethyl acetate. The organic layer was sequentially washed with water (x2) and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:9), and the resulting crystals were recrystallized from diisopropyl ether, to give 1.73 g of the title compound as white needles.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.83 (3H, s), 6.30 (1H, d, J = 8.8 Hz), 7.12 - 7.20 (6H, m), 7.30 - 7.40 (9H, m), 7.55 (1H, dd, J = 6.8, 8.8 Hz)

PRODUCTION EXAMPLE II-13-f

3-Benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-5-indazolecarboxylic acid methyl ester

To a solution of 515 mg of 3-bromo-4-fluoro-1-trityl-1*H*-indazole-5-carboxylic acid methyl ester obtained in Production Example II-13-e in 7.5 ml dimethylformamide were sequentially added 267 mg of 2-benzo[*b*]thiopheneboronic acid, 1 ml of an aqueous solution of 291 mg of potassium fluoride, 30 mg of 2-(di-*tert*-butylphosphino)biphenyl and 12 mg of palladium(II) acetate, and the mixture was stirred at 55°C for 1 hour. The reaction mixture was ice-cooled, and then the precipitated crystals were collected by filtration. The resulting crystals were dissolved in a mixture solution of ethyl acetate and tetrahydrofuran, and the mixture was sequentially washed with water, half-saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated, to give 504 mg of a crude coupling product. A total of 350 mg of the resulting crude coupling product was suspended in 4 ml of methylene chloride, 2 ml of trifluoroacetic acid and 0.1 ml of triisopropylsilane were added, and the mixture was stirred at room temperature for 15 minutes. To the reaction mixture was added

saturated aqueous sodium hydrogencarbonate solution and it was extracted with 50 ml of ethyl acetate. The organic layer was sequentially washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:toluene = 1:9), to give 154 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400MHz, DMSO-D_6) δ 3.91 (3H, s), 7.38-7.45 (2H, m), 7.52 (1H, d, J= 8.8Hz), 7.91 (1H, dd, J=6.8, 8.8Hz), 7.96-8.03 (2H, m), 8.05 (1H, s), 14.01 (1H, s).

PRODUCTION EXAMPLE II-13-g

3-Benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-5-indazolecarboxylic acid

To a solution of 152 mg of 3-benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-5-indazolecarboxylic acid methyl ester obtained in Production Example II-13-f in a mixture of 2 ml of tetrahydrofuran and 2 ml of methanol was added 1 ml of 5 N aqueous sodium hydroxide solution, and the mixture was stirred at 55°C for 2.5 hours. After standing to cool, 5.5 ml of 1 N hydrochloric acid was added and the mixture was extracted with ethyl acetate. The organic layer was sequentially washed with water and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was recrystallized from tetrahydrofuran-ethyl acetate, to give 104 mg of the title compound as pale

red crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.36 - 7.43 (2H, m), 7.47 (1H, d, J=8.8 Hz), 7.88 (1H, dd, J = 6.4, 8.8 Hz), 7.95 - 8.00 (2H, m), 8.03 (1H, s), 13.16 (1H, s).

PRODUCTION EXAMPLE II-14-a

4-Fluoro-3-naphthalen-2-yl-1*H*-5-indazolecarboxylic acid methyl ester

By the procedure of Production Example II-13-f, 495 mg of a Suzuki coupling product was obtained from 515 mg of 3-bromo-4-fluoro-1-trityl-1*H*-indazole-5-carboxylic acid methyl ester obtained in Production Example II-13-e and 258 mg of n-naphthaleneboronic acid. A total of 350 mg of the coupling product was subjected to deprotection (on trityl group) by the procedure of Production Example II-13-f, to give 154 mg of the title compound as bright yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.88 (3H, s), 7.52 (1H, d, J = 8.8 Hz), 7.56 - 7.62 (2H, m), 7.89 (1H, dd, J = 6.4, 8.0 Hz), 7.96 - 8.10 (4H, m) 8.39 (1H, s), 13.94 (1H, s)

PRODUCTION EXAMPLE II-14-b

4-Fluoro-3-naphthalen-2-yl-1*H*-5-indazolecarboxylic acid

A total of 63 mg of the title compound was obtained as bright yellow crystals by the procedure of Production Example II-13-g, except using 152 mg of 4-fluoro-3-naphthalen-2-yl-1*H*-5-indazolecarboxylic acid methyl ester produced in Production Example II-14-a.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.49 (1H, d, J = 8.8 Hz), 7.55 - 7.61

(2H, m), 7.88 (1H, dd, J = 6.4, 8.8 Hz), 7.96 - 8.08 (4H, m), 8.39 (1H, s), 13.08 (1H, s), 13.88 (1H, s).

PRODUCTION EXAMPLE II-15-a

3-Benzo[*b*]furan-2-yl-1*H*-5-indazolecarboxylic acid methyl ester

A total of 123 mg of the title compound was obtained as bright yellow crystals by the procedure of Production Example II-13-f, except from 308 mg of 3-bromo-4-fluoro-1-trityl-1*H*-indazole-5-carboxylic acid methyl ester produced in Production Example II-13-e and 145 mg of 2-benzo[*b*]furanboronic acid.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.91 (3H, s), 7.32 (1H, t, J = 7.6 Hz), 7.39 (1H, dd, J = 7.6, 8.4 Hz), 7.51 (1H, s), 7.54 (1H, d, J = 8.8 Hz), 7.69 (1H, d, J = 8.4 Hz), 7.78 (1H, d, J = 7.6 Hz), 7.91 (1H, dd, J = 6.4, 8.8 Hz), 14.15 (1H, s)

PRODUCTION EXAMPLE II-15-b

3-Benzo[*b*]furan-2-yl-1*H*-5-indazolecarboxylic acid

A total of 115 mg of the title compound was obtained as bright yellow crystals by the procedure of Production Example II-13-f, except from 121 mg of 3-benzo[*b*]furan-2-yl-1*H*-5-indazolecarboxylic acid methyl ester obtained in Production Example II-15-a.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.32 (1H, t, J = 7.6 Hz), 7.39 (1H, dd, J = 7.6, 8.0 Hz), 7.50 (1H, s), 7.50 (1H, d, J = 8.8 Hz), 7.69 (1H, d, J = 8.0 Hz), 7.76 (1H, d, J = 7.6 Hz), 7.90 (1H, dd, J = 6.8, 8.8 Hz), 13.18 (1H, s), 14.09 (1H, s)

PRODUCTION EXAMPLE II-16-a

Benzo[*b*]thiophen-2-yl-(5-bromo-2,4-difluorophenyl)methanone

As a raw material, 17.7 g of 1,5-dibromo-2,4-difluorobenzene obtained in Production Example II-5-a was subjected to lithiation with n-butyllithium by the procedure of Production Example II-5-b, was subjected to formylation with N,N-dimethylformamide, to give 10.7 g of 5-bromo-2,4-difluorobenzaldehyde. This compound was allowed to react with benzothiophene by the procedure of Production Example II-12-a to yield an alcohol, and then the alcohol was oxidized by the procedure of Production Example II-10-b, to give 9.7 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.07 (1H, t, J = 8.6 Hz), 7.44 (1H, t, J = 8.4 Hz), 7.52 (1H, t, J = 8.4 Hz), 7.77 (1H, s), 8.65 (1H, d, J = 6.6 Hz), 13.50-13.60 (1H,bs).

PRODUCTION EXAMPLE II-16-b

5-(Benzo[*b*]thiophen-2-carbonyl)-2,4-difluoro-benzonitrile

A total of 1.46 g of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-1-c, except from 2.98 g of benzo[*b*]thiophen-2-yl-(5-bromo-2,4-difluorophenyl)methanone.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.16 (1H, t, J = 8.8 Hz), 7.44 (1H, t, J = 8.0 Hz), 7.53 (1H, t, J = 8.0 Hz), 7.73 (1H, s), 7.88 (1H, d, J = 8.0 Hz), 7.91 (1H, d, J=8.0Hz).

PRODUCTION EXAMPLE II-16-c

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carbonitrile

A total of 1.08 g of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-10-c, except from 1.46 g of 5-(benzo[*b*]thiophen-2-carbonyl)-2,4-difluoro-benzonitrile.

^1H-NMR (400 MHz, DMSO-d_6) δ 7.37-7.45 (2H, m), 7.74 (1H, d, J = 10.0 Hz), 7.86-7.91 (1H, m), 7.97-8.01 (1H, m), 8.39 (1H, s), 9.06 (1H, d, J = 6.0 Hz).

PRODUCTION EXAMPLE II-16-d

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carboxylic acid

A total of 600 mg of 3-benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carbonitrile obtained in Production Example II-16-c was hydrolyzed by the procedure of Production Example II-1-e, to give 310 mg of the title compound as a light brown powder.

^1H-NMR (400 MHz, DMSO-d_6) δ 7.36-7.43 (2H, m), 7.50 (1H, d, J = 10.9 Hz), 7.97-8.02 (2H, m), 8.16 (1H, s), 8.73 (1H, d, J = 6.9 Hz), 13.15-13.30 (1H, bs), 13.69 (1H, s).

PRODUCTION EXAMPLE II-17-a

(5-Bromo-2,4-difluorophenyl)naphthalene-2-yl-methanone

A total of 13.6 g of 1,5-dibromo-2,4-difluorobenzene obtained in Production Example II-5-a as a raw material was subjected to lithiation with n-butyllithium by the procedure of Production Example II-5-b. This compound was treated with 2-naphthoaldehyde to yield an alcohol, the

alcohol was oxidized by the procedure of Production Example II-10-b, to give 13.5 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.51-7.59 (2H, m), 7.63 (1H, d, J = 9.0 Hz), 7.93-7.96 (1H, m), 8.02 (1H, d, J = 8.4 Hz), 8.14-8.18 (1H, m), 8.15 (1H, dd, J = 1.6, 8.4 Hz), 8.56 (1H, d, J = 1.6 Hz), 8.61 (1H, d, J = 6.5 Hz), 13.45-13.65 (1H, bs).

PRODUCTION EXAMPLE II-17-b

2,4-Difluoro-5-(naphthalene-2-carbonyl)-benzonitrile

A total of 2.3 g of the title compound was obtained as a colorless powder by the procedure of Production Example II-1-c, except from 3.76 g of (5-bromo-2,4-difluorophenyl)naphthalene-2-yl-methanone.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.15 (1H, t, J = 8.8 Hz), 7.60 (1H, t, J = 7.8 Hz), 7.67 (1H, t, J = 7.8 Hz), 7.91-7.97 (4H, m), 7.97 (1H, t, J = 7.0 Hz), 8.19 (1H, s).

PRODUCTION EXAMPLE II-17-c

6-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carbonitrile

A total of 2.1 g of 2,4-difluoro-5-(naphthalene-2-carbonyl)-benzonitrile was allowed to react with hydrazine monohydrate by the procedure of Production Example II-10-c and thereby yielded 1.6 g of the title compound as a colorless powder.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.53-7.61 (2H, m), 7.72 (1H, d, J = 9.6 Hz), 7.93-7.98 (1H, m), 8.03 (1H, d, J = 8.5 Hz),

8.14-8.19 (1H, m), 8.18 (1H, d, J = 8.5 Hz), 8.65 (1H, s), 9.03 (1H, d, J = 6.0 Hz), 13.83-13.97 (1H, bs).

PRODUCTION EXAMPLE II-17-d

6-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid

A total of 700 mg of 6-fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carbonitrile obtained in Production Example II-17-c was hydrolyzed by the procedure of Production Example II-1-e and thereby yielded 610 mg of the title compound as a colorless powder.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.47 (1H, d, J = 11.3 Hz), 7.53-7.60 (2H, m), 7.94-7.99 (1H, m), 8.07 (1H, d, J = 8.6 Hz), 8.09-8.14 (1H, m), 8.11 (1H, d, J = 8.6 Hz), 8.50 (1H, s), 8.67 (1H, d, J = 7.2 Hz), 13.05-13.25 (1H, bs), 13.62 (1H, s).

PRODUCTION EXAMPLE II-18-a

5-Bromo-3-(3-fluoro-phenyl)-4-methoxy-1-trityl-1*H*-indazole

A total of 530 mg of 5-bromo-3-(3-fluoro-phenyl)-4-methoxy-1*H*-indazole obtained in Production Example II-2-c was dissolved in 8.3 ml of dimethylformamide, and 99 mg of sodium hydride (60% content) was added under ice-cooling and stirring. After stirring for 15 minutes, 483 mg of triphenylmethyl chloride was added. After stirring at room temperature for 1 hour, saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated.

The crude product was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:8), to give 998 mg of the title compound as pale yellow crystals.
^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.54 (3H, s), 6.16 (1H, d, J = 8.8 Hz), 7.01 - 7.08 (1H, m), 7.11 (1H, d, J = 8.8 Hz), 7.16 - 7.40 (16H, m), 7.64 - 7.69 (1H, m), 7.74 (1H, d, J = 8.0 Hz).

PRODUCTION EXAMPLE II-18-b

3-(3-Fluoro-phenyl)-4-methoxy-1-trityl-1*H*-indazol-5-ylamine

A total of 810 mg of 5-bromo-3-(3-fluoro-phenyl)-4-methoxy-1-trityl-1*H*-indazole obtained in Production Example II-18-a was dissolved in 7.2 ml of toluene, 194 mg of sodium t-butoxide, 0.29 ml of benzophenoneimine, 135 mg of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and 74.5 mg of tris(dibenzylideneacetone)bispalladium were added, and the mixture was stirred at 80°C in an atmosphere of nitrogen gas for 8 hours. The reaction mixture was cooled to room temperature, and diethyl ether was added. The mixture was filtrated through Celite, and the filtrate was evaporated. The resulting residue was dissolved in 7.2 ml of tetrahydrofuran and 0.36 ml of 2 N hydrochloric acid was added, followed by stirring at room temperature for 3 hours. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture and the mixture was extracted with diethyl ether, The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by

silica gel column chromatography (ethyl acetate:hexane = 1:3), to give 426 mg of the title compound as reddish brown crystals.

^{1}H-NMR (400MHz, $CDCl_3$) δ 3.46 (3H, s), 6.11 (1H, d, J=8.8Hz), 6.55 (1H, d, J=8.8Hz), 6.96 - 7.04(1H, m), 7.20 - 7.62(16H, m), 7.68 - 7.74(1H, m), 7.76 (1H, d, J=8.0Hz).

PRODUCTION EXAMPLE II-19-a

4-Fluoro-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazole-5-carboxylic acid

A total of 1.29 g of the title compound was obtained as an ocher yellow amorphous substance by the procedure of Production Example II-18-a, except from 1.25 g of 4-fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid obtained in Production Example II-3-d.

^{1}H-NMR (400 MHz, CD_3OD) δ 6.34 (1H, d, J = 9.2 Hz), 7.08 - 7.16 (1H, m), 7.16 - 7.37 (16H, m), 7.38 - 7.67 (3H, m).

PRODUCTION EXAMPLE II-19-b

{4-Fluoro-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazol-5-yl}-carbamic acid benzyl ester

A total of 1.29 g of 4-fluoro-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazole-5-carboxylic acid obtained in Production Example II-19-a was dissolved in 12.5 ml of toluene. Under stirring at room temperature, 0.38 ml of triethylamine and 0.566 ml of diphenylphosphoryl azide were added, and the mixture was stirred at room temperature for 2 hours and at 120°C for further 1.5 hours. To the reaction mixture was

added 0.776 ml of benzyl alcohol, followed by stirring at 120°C for 1.5 hours. After cooling to room temperature, the reaction mixture was added with water, and extracted with ethyl acetate. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:5), to give 652 mg of the title compound as an ocher yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.19 (2H, s), 6.23 (1H, d, J = 9.2 Hz), 6.70 - 7.71 (26H, m)

PRODUCTION EXAMPLE II-19-c

4-Fluoro-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazol-5-yl-amine

A total of 652 mg of {4-fluoro-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazol-5-yl}-carbamic acid benzyl ester obtained in Production Example II-19-b was dissolved in 20 ml of methanol, 652 mg of 10% palladium-carbon, and the mixture was subjected to catalytic hydrogenation at room temperature at normal pressure. After stirring for 4 hours, the mixture was filtered through Celite, and the filtrate was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:5), to give 297 mg of the title compound.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.54 (2H, brs), 6.09 (1H, d, J = 8.8 Hz), 6.56 (1H, t, J = 8.8 Hz), 6.96 - 7.40 (17H, m), 7.51 (1H, d, J = 10.4 Hz), 7.69 (1H, d, J = 7.6 Hz)

PRODUCTION EXAMPLE II-20-a

6-Fluoro-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazole-5-carboxylic acid

A total of 496 mg of the title compound was obtained as ocher yellow crystals by the procedure of Production Example II-18-a, except from 352 mg of 6-fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid obtained in Production Example II-5-f.

^{1}H-NMR (400MHz, $CDCl_3$) δ 6.13 (1H, d, J = 12.8 Hz), 6.96 - 7.78 (19H, m), 8.73 (1H, d, J = 10.4 Hz).

PRODUCTION EXAMPLE II-20-b

{6-Fluoro-3-(fluoro-phenyl)-1-trityl-1*H*-indazol-5-yl}-carbamic acid benzyl ester

A total of 760 mg (crude purified product) was obtained by the procedure of Production Example II-19-b, except from 496 mg of 6-fluoro-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazole-5-carboxylic acid obtained in Production Example II-20-a.

^{1}H-NMR (400MHz, $CDCl_3$) δ 5.24 (2H, s), 6.09 (1H, d, J = 12.0 Hz), 6.80 - 6.86 (1H, brs), 7.00 - 7.07 (1H, m), 7.14 - 7.46 (22H, m), 7.54 - 7.60 (1H, m), 7.65 - 7.73 (1H, m)

PRODUCTION EXAMPLE II-20-C

6-Fluoro-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazol-5-yl-amine

A total of 185 mg of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-19-c, except from 760 mg of {6-fluoro-3-(3-

fluoro-phenyl)-1-trityl-1*H*-indazol-5-yl}-carbamic acid benzyl ester obtained in Production Example II-20-b.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.65 (2H, brs), 6.06 (1H, d, J=12.0Hz), 6.97-7.05 (1H, m), 7.16 - 7.44 (17H, m), 7.54 (1H, d, J=6.0 Hz), 7.63 (1H, d, J = 7.2 Hz)

PRODUCTION EXAMPLE II-21

4-Bromo-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazol-5-yl-amine

A total of 1.04 g of 3-(3-fluoro-phenyl)-1-trityl-1*H*-indazol-5-ylamine was dissolved in 22.3 ml of dichloromethane, and 375 mg of sodium hydrogencarbonate was added. Under ice-cooling and stirring, a solution of 0.12 ml of bromine in 50 ml dichloromethane was added dropwise over 50 minutes. After stirring for 2 hours while ice-cooling, saturated aqueous sodium thiosulfate solution and the mixture was extracted with diethyl ether. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:5), to give 1.18 g of the title compound as a white foam.

^{1}H-NMR (400MHz, $CDCl_3$) δ 3.97 (2H, brs), 6.31 (1H, d, J = 8.8 Hz), 6.52 (1H, d, J = 8.8 Hz), 7.02 - 7.09 (1H, m), 7.18 - 7.43 (18H, m).

PRODUCTION EXAMPLE II-22-a

5-Bromo-3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazole

A total of 2.68 g of the title compound was obtained as pale yellow crystals by the procedure of Production

Example II-1-d, except from 5.05 g of (5-bromo-2-fluoro-4-methoxy-phenyl)-(3-fluoro-phenyl)-methanone obtained in Production Example II-1-b.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.94 (3H, s), 6.85 (1H, s), 7.09 - 7.16 (1H, m), 7.48 (1H, td, J = 8.0, 6.0 Hz), 7.61 - 7.66 (1H, m), 7.68 - 7.74 (1H, m), 8.17 (1H, s).

PRODUCTION EXAMPLE II-22-b

5-Bromo-3-(3-fluoro-phenyl)-6-methoxy-1-trityl-1*H*-indazole

A total of 1.64 g of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-18-a, except from 914 mg of 5-bromo-3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazole obtained in Production Example II-22-a.

^{1}H-NMR (400MHz, $CDCl_3$) δ 3.38 (3H, s), 5.74 (1H, s), 7.00 - 7.06 (1H, m), 7.14 - 7.36 (15H, m), 7.40 (1H, td, J = 8.0, 6.0 Hz), 7.55 (1H, d, J = 10.4 Hz), 7.65 (1H, d, J = 8.0 Hz), 8.15 (1H, s)

PRODUCTION EXAMPLE II-22-c

3-(3-Fluoro-phenyl)-6-methoxy-1-trityl-1*H*-indazol-5-ylamine

A total of 526 mg of the title compound was obtained as an ocher yellow amorphous substance by the procedure of Production Example II-18-b, except from 674 mg of 5-bromo-3-(3-fluoro-phenyl)-6-methoxy-1-trityl-1*H*-indazole obtained in Production Example II-22-b.

^{1}H-NMR (400MHz, $CDCl_3$) δ 3.37 (3H, s), 3.77 (2H, brs), 5.65 (1H, s), 6.95-7.02 (1H, m), 7.17 - 7.40 (17H, m), 7.57 (1H, d, J=10.4 Hz), 7.67

(1H, d, J=8.0 Hz)

PRODUCTION EXAMPLE II-23

3-(3-Fluoro-phenyl)-7-methyl-1-trityl-1*H*-indazol-5-ylamine

To a solution of 2.0 g of 5-bromo-3-(3-fluorophenyl)-7-methyl-1-trityl-1*H*-indazole obtained in Production Example II-9-c in 20 ml toluene at room temperature were added 0.73 g of benzophenoneimine, 95 mg of tris(dibenzylideneacetone)(chloroform)dipalladium(0), 0.17 g of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and 0.53 g of sodium *tert*-butyrate, and the mixture was heated under reflux for one day. The mixture was diluted with water and ethyl acetate, and the organic layer was sequentially washed with saturated aqueous ammonium chloride solution and brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was dissolved in 30 ml of tetrahydrofuran, 10 ml of 5 N hydrochloric acid was added at room temperature, and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was neutralized with 5 N aqueous sodium hydroxide solution and was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (ethyl acetate:n-hexane = 1:10 to 1:3), and the resulting obtained crystals were washed with diethyl ether, to give 0.86 g of the title compound as colorless

crystals.

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.38 (3H, s), 3.61 (2H, brs), 6.45 (1H, dd, J=2.4, 0.8Hz), 6.95 (1H, dt, J=0.8, 8.0Hz), 7.12-7.31 (16H, m), 7.32 (1H, dt, J=6.0, 8.0Hz), 7.43 (1H, ddd, J = 1.2, 2.4, 10.4 Hz), 7.55 (1H, dt, J = 1.2, 8.0 Hz)

PRODUCTION EXAMPLE II-24-a

3-Benzo[*b*]thiophen-2-yl-5-bromo-6-fluoro-1*H*-indazole

A total of 5.7 g of benzo[*b*]thiophen-2-yl-(5-bromo-2,4-difluorophenyl)methanone obtained in Production Example II-16-a was allowed to react with hydrazine monohydrate by the procedure of Production Example II-10-c and thereby yielded 0.6 g of the title compound as a colorless powder.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.34-7.43 (2H, m), 7.65 (1H, d, J = 8.8 Hz), 7.90 (1H,bd,J=7.6Hz), 7.97 (1H, bd, J = 7.6 Hz), 8.28 (1H, s), 8.65 (1H,d,J=6.6Hz), 13.50-13.60 (1H, bs).

PRODUCTION EXAMPLE II-24-b

3-Benzo[*b*]thiophen-2-yl-5-bromo-6-fluoro-1-trityl-1*H*-indazole

A total of 350 mg of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-18-a, except from 269 mg of 3-benzo[*b*]thiophen-2-yl-5-bromo-6-fluoro-1*H*-indazole.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.12 (1H, d, J = 9.6 Hz), 7.18-7.38 (15H, m), 7.73-7.84 (5H, m), 8.27 (1H, d, J = 6.4 Hz).

PRODUCTION EXAMPLE II-24-c

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1-trityl-1*H*-indazol-5-ylamine

A total of 280 mg of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-1-c, except from 350 mg of 3-benzo[*b*]thiophen-2-yl-5-bromo-6-fluoro-1-trityl-1*H*-indazole.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 5.88 (1H, d, J=12.4Hz), 7.12-7.42 (17H, m), 7.47 (1H, d, J=8.4Hz), 7.82 (1H, s), 7.86 (1H, d, J=6.8Hz), 7.93 (1H, d, J=6.8Hz).

PRODUCTION EXAMPLE II-25-a

5-Bromo-6-fluoro-3-naphthalen-2-yl-1*H*-indazole

A total of 7.0 g of (5-bromo-2,4-difluorophenyl)naphthalene-2-yl-methanone obtained in Production Example II-17-a was allowed to react with hydrazine monohydrate by the procedure of Production Example II-10-c and thereby yielded 1.5 g of the title compound as a colorless powder.

^{1}H-NMR (400MHz, DMSO-d_6) δ 7.51-7.59 (2H, m), 7.63 (1H, d, J=9.0Hz), 7.93-7.96 (1H, m), 8.02 (1H, d, J=8.4Hz), 8.14-8.18 (1H, m), 8.15 (1H,dd,J=1.6,8.4Hz), 8.56 (1H, d, J = 1.6 Hz), 8.61 (1H, d, J = 6.5 Hz), 13.45-13.65 (1H, bs).

PRODUCTION EXAMPLE II-25-b

5-Bromo-6-fluoro-3-naphthalen-2-yl-1-trityl-1*H*-indazole

A total of 1.22 g of the title compound was obtained as white crystals by the procedure of Production Example II-18-a, except from 811 mg of 5-bromo-6-fluoro-3-

naphthalen-2-yl-1*H*-indazole.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.17 (1H, d, J = 10.0 Hz), 7.21-7.35 (15H, m), 7.45-7.54 (2H, m), 7.81-7.97 (4H, m), 8.26-8.31(2H, m).

PRODUCTION EXAMPLE II-25-c

6-Fluoro-3-naphthalen-2-yl-1-trityl-1*H*-indazol-5-ylamine

A total of 970 mg of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-1-c, except from 1.22 g of 5-bromo-6-fluoro-3-naphthalen-2-yl-1-trityl-1*H*-indazole.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 5.94 (1H, d, J = 12.0 Hz), 7.20-7.40 (15H, m), 7.47-7.59 (3H, m), 7.86-8.00 (4H, m), 8.31 (1H, s).

PRODUCTION EXAMPLE II-26

C-(3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl)-methylamine

A total of 71 mg of lithium aluminium hydride was suspended in 4.7 ml of tetrahydrofuran, 249 mg of aluminium chloride was added under ice-cooling, and the mixture was stirred for 10 minutes. To the reaction mixture was added 50 mg of 3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazole-5-carbonitrile obtained in Production Example II-1-d, followed by stirring at room temperature for 3 hours. The reaction mixture was ice-cooled, 27% aqueous ammonia was added and the mixture was filtrated through Celite. The filtrate was evaporated, and the residue was purified and separated by silica gel column chromatography (NH silica gel) (ethyl acetate), to give 108 mg of the title compound.

^{1}H-NMR (400MHz, CD_3OD) δ 4.02 (3H, s), 4.25 (2H, s), 7.10 - 7.19 (2H, m), 7.54 (1H, td, 8.0, 6.0 Hz), 7.63 - 7.69 (1H, m), 7.78 (1H, d, 8.0 Hz)

PRODUCTION EXAMPLE II-27-a

4-Fluoro-3-(3-fluoro-benzoyl)-2-methoxy-benzonitrile

A total of 399 mg of the title compound was obtained as a pale yellow oil by the procedure of Production Example II-1-c, except from 2.07 g of (3-bromol-6-fluoro-2-methoxy-phenyl)-(3-fluoro-phenyl)-methanone obtained in Production Example II-2-b.

^{1}H-NMR(400MHz, $CDCl_3$) δ 4.00 (3H, s), 7.01 (1H, t, J = 8.0 Hz), 7.32-7.76 (5H, m).

PRODUCTION EXAMPLE II-27-b

3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazole-5-carbonitrile

A total of 364 mg of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-1-d, except from 399 mg of 4-fluoro-3-(3-fluoro-benzoyl)-2-methoxy-benzonitrile obtained in Production Example II-27-a.

^{1}H-NMR (400MHz, $CDCl_3$) δ 3.94 (3H, s), 7.13-7.29 (2H, m), 7.47 (1H, td, J=8.0, 6.0Hz), 7.52 (1H, d, J=8.8Hz), 7.61-7.66 (1H, m), 7.67-7.72 (1H, m).

PRODUCTION EXAMPLE II-27-c

C-[3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazol-5-yl]-methylamine

A total of 25.8 mg of the title compound was obtained

by the procedure of Production Example II-26, except from 50 mg of 3-(3-fluoro-phenyl)-4-methoxy-1*H*-indazole-5-carbonitrile obtained in Production Example II-27-b.

^{1}H-NMR (400MHz, CD_3OD) δ 3.92 (5H, s), 7.10 - 7.18 (1H, m), 7.31 (1H, d, J=8.4Hz), 7.43 (1H, d, J=8.4Hz), 7.44-7.80 (3H, m). 7.47 (1H, td, J=8.0, 6.0Hz), 7.52 (1H, d, J=8.8Hz), 7.61-7.66 (1H, m), 7.67-7.72 (1H, m).

PRODUCTION EXAMPLE II-28

C-(6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl)-methylamine

A total of 120 mg of the title compound was obtained as ocher yellow crude crystals by the procedure of Production Example II-26, except from 100 mg of 6-fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carbonitrile obtained in Production Example II-5-e.

^{1}H-NMR (400MHz, CD_3OD) δ 4.34 (2H, s), 7.08-7.24 (1H, m), 7.42 (1H, d, J=10.6Hz), 7.56 (1H, td, J=8.0, 6.0Hz), 7.67-7.74 (1H, m), 7.80-7.85 (1H, m), 8.26 (1H, d, J=7.2Hz)

PRODUCTION EXAMPLE II-29

C-(3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-yl)-methylamine

A total of 394 mg of the title compound was obtained as yellow crude crystals by the procedure of Production Example II-26, except from 300 mg of 3-benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carbonitrile obtained in Production Example II-16-c.

^{1}H-NMR (400MHz, DMSO-d_6) δ 4.23 (2H, s), 7.37-7.46 (2H, m), 7.53 (1H, d, J = 10.4 Hz), 7.89 (1H, d, J = 7.2 Hz), 8.00 (1H, d, J = 7.2 Hz), 8.23 (1H, s), 8.62 (1H, d, J = 7.2 Hz).

PRODUCTION EXAMPLE II-30

C-(3-Naphthalen-2-yl-6-fluoro-1*H*-indazol-5-yl)-methylamine

A total of 495 mg of the title compound was obtained by the procedure of Production Example II-26, except from 300 mg of 6-fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carbonitrile obtained in Production Example II-17-c.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 4.23 (2H, s), 7.51 (1H, d, J = 10.0 Hz), 7.52-7.64 (2H, m), 7.97 (1H, d, J = 8.8 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.14-8.21 (2H, m), 8.62 (1H, d, J = 7.2 Hz), 8.65 (1H, s).

PRODUCTION EXAMPLE II-31-a

(6-Bromo-2,3-difluorophenyl)trimethylsilyl

In an atmosphere of nitrogen gas, 66.0 ml of a 1.57 M solution of n-butyllithium in hexane was added to a solution of 18.2 ml of *N,N*-diisopropylamine in 200 ml tetrahydrofuran at 0°C, and the mixture was stirred at the same temperature for 10 minutes. After cooling to -78°C, a solution of 20.0 g of 1-bromo-3,4-difluorobenzene in 100 ml tetrahydrofuran was added dropwise. After stirring at the same temperature for 30 minutes, 32.9 ml of chlorotrimethylsilane was added dropwise, the temperature was gradually raised to room temperature and the mixture was stirred for one day. The reaction mixture was diluted

with water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The crude product was purified and separated by silica gel column chromatography (n-hexane), to give 20.3 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.47 (9H, s), 6.99 (1H, dt, J = 9.6, 8.8 Hz), 7.27 (1H, ddd, J = 2.0, 4.0, 8.8 Hz).

PRODUCTION EXAMPLE II-31-b

(5-Bromo-2,3-difluorophenyl)-(3-fluorophenyl)methanone

A total of 5.0 g of (6-bromo-2,3-difluorophenyl)trimethylsilyl was allowed to react with 3-fluoro-benzaldehyde by the procedure of Production Example II-2-a. The resulting crude product was dissolved in 50 ml of dimethylformamide and 5 ml of water, cesium fluoride was added at room temperature, and the mixture was stirred at the same temperature for 3 hours. The reaction mixture was diluted with ethyl acetate, and the organic layer was sequentially washed with saturated aqueous ammonium chloride solution and brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The resulting crude product was oxidized by the procedure of Production Example II-8-b, to give 4.52 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, ddt, J = 1.2, 2.4, 8.0 Hz), 7.43 (1H, td, J = 2.4, 5.2 Hz), 7.48 (1H, dt, J = 5.2, 8.0 Hz), 7.50-7.58 (4H, m).

PRODUCTION EXAMPLE II-31-c

3,4-Difluoro-5-(3-fluorobenzoyl)benzonitrile

A total of 3.5 g of the title compound was obtained as a pale yellow oil by the procedure of Production Example II-9-d, except from 4.5 g of (5-bromo-2,3-difluorophenyl)-(3-fluorophenyl)methanone.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, ddd, J = 1.2, 2.4, 8.0 Hz), 7.47-7.55 (3H, m), 7.63-7.71 (2H, m).

PRODUCTION EXAMPLE II-31-d

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carbonitrile

A total of 3.2 g of the title compound was obtained as colorless crystals by the procedure of Production Example II-1-d, except from 3.5 g of 3,4-difluoro-5-(3-fluorobenzoyl)benzonitrile.

^{1}H-NMR (400 MHz, CD_3OD) δ 7.20 (1H, dd, J = 2.0, 8.0 Hz), 7.49 (1H, dd, J = 1.2, 10.4 Hz), 7.56 (1H, dt, J = 6.0, 8.0 Hz), 7.69 (1H, td, J = 2.0, 10.4 Hz), 7.78 (1H, d, J = 8.0 Hz), 8.33 (1H, d, J = 1.2 Hz).

PRODUCTION EXAMPLE II-31-e

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid

A total of 2.1 g of the title compound was obtained as colorless crystals by the procedure of Production Example II-1-e, except from 3.2 g of 7-fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carbonitrile.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.31 (1H, ddd, J = 1.2, 2.4, 8.0 Hz), 7.62 (1H, dt, J = 6.0, 8.0 Hz), 7.70 (1H, dd, J = 1.2, 11.6 Hz), 7.72 (1H, ddd, J = 1.2, 2.4, 10.0 Hz), 7.81 (1H, dt, J = 1.2, 8.0 Hz), 8.44 (1H,

d, J = 1.2 Hz).

PRODUCTION EXAMPLE II-32-a

(5-Bromo-2,3-difluorophenyl)naphthalen-2-ylmethanone

A total of 5.5 g of the title compound was obtained as colorless crystals by the procedure of Production Example II-31-a, except from 5.0 g of (6-bromo-2,3-difluorophenyl)trimethylsilyl.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, td, J = 2.0, 8.8 Hz), 7.52-7.59 (2H, m), 7.64 (1H, dt, J = 1.2, 8.0 Hz), 7.88-7.98 (4H, m), 8.23 (1H, s).

PRODUCTION EXAMPLE II-32-b

3,4-Difluoro-5-(naphthalen-2-carbonyl)benzonitrile

A total of 2.94 g of the title compound was obtained as colorless crystals by the procedure of Production Example II-9-d, except from 5.5 g of (5-bromo-2,3-difluorophenyl)naphthalen-2-ylmethanone.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, dt, J = 1.2, 8.0 Hz), 7.64-7.72 (3H, m), 7.90-7.96 (4H, m), 8.19 (1H, s).

PRODUCTION EXAMPLE II-32-c

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carbonitrile

A total of 2.60 g of the title compound was obtained as colorless crystals by the procedure of Production Example II-1-d, except from 2.94 g of 3,4-difluoro-5-(naphthalen-2-carbonyl)benzonitrile.

^{1}H-NMR (400 MHz, CD_3OD) δ 7.48-7.56 (3H, m), 7.88-7.93 (1H, m), 7.98-8.11 (3H, m), 8.44 (1H, s), 8.47 (1H, d, J = 0.8 Hz).

PRODUCTION EXAMPLE II-32-d

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid

To 1.0 g of 7-fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carbonitrile were sequentially added 5.0 ml of glacial acetic acid, 5.0 ml of water and 10.0 ml of concentrated sulfuric acid, and the mixture was stirred at 120°C for one day. After standing to cool, 20 ml of water was added to the reaction mixture and the resulting crystals were collected by filtration. The crystals were sequentially washed with water and diethyl ether, to give 1.0 g of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.55-7.60 (2H, m), 7.71 (1H, dd, J = 0.8, 11.2 Hz), 7.96-7.99 (1H, m), 8.08-8.14 (3H, m), 8.51 (1H, s), 8.59 (1H, d, J = 0.8 Hz).

PRODUCTION EXAMPLE II-33-a

3-Benzo[*b*]thiophen-2-yl-4-fluoro-1-trityl-1*H*-5-indazolecarboxylic acid

To a solution of 149 mg of the coupling product (3-benzo[*b*]thiophen-2-yl-4-fluoro-1-trityl-1*H*-5-indazolecarboxylic acid methyl ester) obtained in Production Example II-13-f in a solvent mixture of 4 ml of tetrahydrofuran and 1 ml of methanol was added 0.5 ml of 5 N aqueous sodium hydroxide solution, and the mixture was stirred at 50°C for 2 hours. To the reaction mixture was added 3 ml of 1 N hydrochloric acid and the mixture was extracted with 20 ml of ethyl acetate. The organic layer

was sequentially washed with water and brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated, to give 145 mg of the title compound as yellow crystals.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 6.29 (1H, dd J = 1.2, 8.8 Hz), 7.14 - 7.23 (6H, m), 7.27 - 7.42 (11H, m), 7.55 (1H, t, J = 8.8 Hz), 7.91 - 7.97 (2H, m), 8.02 (1H, s), 13.19 (1H, s).

PRODUCTION EXAMPLE II-33-b

{3-Benzo[*b*]thiophen-2-yl-4-fluoro-1-trityl-1*H*-indazol-5-yl}carbamic acid benzyl ester

A total of 73 mg of the title compound was obtained as a colorless viscous oil by the procedure of Production Example II-19-b, except from 143 mg of 3-benzo[*b*]thiophen-2-yl-4-fluoro-1-trityl-1*H*-5-indazolecarboxylic acid obtained in Production Example II-33-a.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 5.14 (2H, s), 6.23 (1H, d, J = 8.8Hz), 7.13 - 7.45 (23H, m), 7.89 - 7.99 (3H, m), 9.43 (1H, s).

PRODUCTION EXAMPLE II-33-c

3-Benzo[*b*]thiophen-2-yl-4-fluoro-1-trityl-1*H*-indazol-5-ylamine

A total of 52 mg of the title compound was obtained as bright yellow crystals by the procedure of Production Example II-19-c, except from 68 mg of {3-benzo[*b*]thiophen-2-yl-4-fluoro-1-trityl-1*H*-indazol-5-yl}carbamic acid benzyl ester produced in Production Example II-33-b.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 5.00 (2H, s), 6.00 (1H, d, J = 8.8 Hz), 6.69 (1H, t, J = 8.8 Hz), 7.10 - 7.40 (17H, m), 7.83 - 7.93

(3H, m)

PRODUCTION EXAMPLE II-34-a

4-Fluoro-3-naphthalen-2-yl-1-trityl-1*H*-5-indazolecarboxylic acid

A total of 127 mg of the title compound was obtained as yellow crystals by the procedure of Production Example II-33-a, except from 139 mg of the coupling product (4-fluoro-3-naphthalen-2-yl-1-trityl-1*H*-5-indazolecarboxylic acid methyl ester) produced in Production Example II-14-a.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 6.34 (1H, dd, J = 0.8, 8.8 Hz), 7.18 - 7.40 (16H, m), 7.50 - 7.60 (2H, m), 7.84 (1H, d, J = 8.4 Hz), 7.93 - 8.08 (3H, m), 8.30 (1H, s), 13.09 (1H, s)

PRODUCTION EXAMPLE II-34-b

(4-Fluoro-3-naphthalen-2-yl-1-trityl-1*H*-indazol-5-yl)carbamic acid benzyl ester

A total of 54 mg of the title compound was obtained as a colorless viscous oil by the procedure of Production Example II-19-b, except from 125 mg of 4-fluoro-3-naphthalen-2-yl-1-trityl-1*H*-5-indazolecarboxylic acid obtained in Production Example II-34-a.

^{1}H-NMR (400 MHz, DMSO-D_5) δ 5.11 (2H, s), 6.27 (1H, d, J = 8.8 Hz), 7.20 - 7.45 (21H, m), 7.52 - 7.58 (2H, m), 7.83 (1H, d, J = 8.4 Hz), 7.92 - 8.00 (3H, m), 8.26 (1H, s), 9.35 (1H, s).

PRODUCTION EXAMPLE II-34-c

4-Fluoro-3-naphthalen-2-yl-1-trityl-1*H*-indazol-5-ylamine

A total of 41 mg of the title compound was obtained as

pale red crystals by the procedure of Production Example II-19-c, except from 54 mg of {4-fluoro-3-naphthalen-2-yl-1-trityl-1*H*-indazol-5-yl}carbamic acid benzyl ester produced in Production Example II-34-b.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 4.92 (2H, s), 6.07 (1H, d, J = 8.8 Hz), 6.70 (1H, t, J = 8.8 Hz), 7.20 - 7.40 (15H, m), 7.51 - 7.58 (2H, m), 7.86 (1H, d, J = 8.8 Hz), 7.91 - 7.98 (3H, m) 8.28 (1H, s)

PRODUCTION EXAMPLE II-35-a

1-Bromo-4-fluoro-2-propoxy-benzene

A total of 5 g of 2-bromo-5-fluoro-phenol was dissolved in 66 ml of N,N-dimethylformamide. Under ice-cooling, 5.42 g of potassium carbonate and 3.07 ml of iodopropane were added, and the mixture was stirred at room temperature for 10 hours. Water was added to the reaction mixture, followed by extracting with diethyl ether. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated, to give 8.29 g of the title compound as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, t, J = 7.2 Hz), 1.80-1.93 (2H, m), 3.95 (2H, t, J = 6.0 Hz), 6.54 (1H, td, J = 8.8, 2.4 Hz), 6.61 (1H, dd, J = 10.8, 2.4 Hz), 7.44 (1H, dd, J = 8.8, 6.0 Hz)

PRODUCTION EXAMPLE II-35-b

Benzo[*b*]furan-2-yl-(3-bromo-6-fluoro-2-propoxy-phenyl)-methanol

A total of 5.59 g of the title compound was obtained

as a pale yellow oil by the procedure of Production Example II-2-a, except from 3 g of 1-bromo-4-fluoro-2-propoxy-benzene.

^{1}H-NMR (400MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.2 Hz), 1.80-1.93 (2H, m), 3.95 (2H, t, J = 6.4 Hz), 6.29 (1H, d, J = 9.2 Hz), 6.84 (1H, t, J = 9.2 Hz), 7.16-7.76 (6H, m)

PRODUCTION EXAMPLE II-35-c

Benzo[*b*]furan-2-yl-(3-bromo-6-fluoro-2-propoxy-phenyl)-methanone

A total of 1.46 g of the title compound was obtained as a yellow oil by the procedure of Production Example II-2-b, except from 5.59 g of benzo[*b*]furan-2-yl-(3-bromo-6-fluoro-2-propoxy-phenyl)-methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.2 Hz), 1.61-1.72 (2H, m), 3.96 (2H, t, J = 6.8 Hz), 6.87 (1H, t, J = 9.2 Hz), 7.29-7.70 (6H, m)

PRODUCTION EXAMPLE II-35-d

3-Benzo[*b*]furan-2-yl-5-bromo-4-propoxy-1*H*-indazole

A total of 801 mg of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-10-c, except from 1.46 g of benzo[*b*]furan-2-yl-(3-bromo-6-fluoro-2-propoxy-phenyl)-methanone.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 0.92 (3H, t, J = 7.2 Hz), 1.65-1.78 (2H, m), 3.77 (2H, t, J = 6.4 Hz), 7.28 (1H, t, J = 7.2 Hz), 7.33-7.38 (1H, m), 7.36 (1H, d, J = 8.8 Hz), 7.44 (1H, s), 7.59 (1H, d, J = 8.8 Hz), 7.64 (1H, d, J = 8.8 Hz), 7.72 (1H, d, J = 8.8 Hz)

PRODUCTION EXAMPLE II-35-e

3-Benzo[*b*]furan-2-yl-4-propoxy-1*H*-indazole-5-carboxylic acid

A total of 45 mg of the title compound was obtained by the procedure of Production Example II-10-d, except from 326 mg of 3-benzo[*b*]furan-2-yl-5-bromo-4-propoxy-1*H*-indazole.

^{1}H-NMR (400 MHz, CD_3OD) δ 0.86 (3H, t, J = 7.2 Hz), 1.70-1.81 (2H, m), 3.95 (2H, t, J = 7.2 Hz), 7.27 (1H, t, J = 7.6 Hz), 7.32-7.38 (2H, m), 7.53 (1H, s), 7.58 (1H, d, J = 7.6 Hz), 7.68 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 8.8 Hz)

Production Example II-36-a

7-Fluoro-3-(3-fluorophenyl)-1-trityl-1*H*-indazole-5-carboxylic acid

A total of 1.4 g of the title compound was obtained as colorless crystals by the procedure of Production Example II-9-c, except from 1.0 g of 7-fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid obtained in Production Example II-31-e.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.10-7.13 (5H, m), 7.25-7.35 (11H, m), 7.45 (1H, d, J = 12.0 Hz), 7.53 (1H, d, J = 8.0 Hz), 7.59 (1H, dt, J = 6.4, 8.0 Hz), 7.69 (1H, d, J = 8.0 Hz), 8.44 (1H, d, J = 1.2 Hz).

Production EXAMPLE II-36-b

7-Fluoro-3-(3-fluorophenyl)-1-trityl-1*H*-indazol-5-ylamine

To a solution of 1.0 g of 7-fluoro-3-(3-fluorophenyl)-1-trityl-1*H*-indazole-5-carboxylic acid in 20 ml toluene at room temperature were added 0.40 ml of triethylamine and

0.46 ml of diphenylphosphoryl azide, the mixture was stirred at the same temperature for 2 hours and at 120°C for 1.5 hours. To the reaction mixture was added 1.0 ml of benzyl alcohol, followed by stirring at 120°C for 1.5 hours. After cooling to room temperature, water was added to the reaction mixture was and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and the solvent was evaporated. To a solution of the resulting crude product in a solvent mixture of 20 ml of methanol and 10 ml of tetrahydrofuran was added 1.0 g of 10% palladium-carbon at room temperature, and the mixture was subjected to catalytic hydrogenation at the same temperature and at normal atmospheric pressure. After stirring for 4 hours, the reaction mixture was filtrated through Celite, the filtrate was evaporated, and the residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane=1:5), to give 540 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 5.19 (2H, d, J = 8.4 Hz), 6.33 (1H, dd, J = 1.6, 14.0 Hz), 6.95 (1H, d, J = 1.6 Hz), 7.08-7.41 (16H, m), 7.42 (1H, ddd, J = 1.2, 1.6, 10.0 Hz), 7.49 (1H, dt, J = 6.0, 10.0 Hz), 7.56 (1H, d, J = 8.0 Hz).

PRODUCTION EXAMPLE II-37-a

7-Fluoro-3-naphthalen-2-yl-1-trityl-1*H*-indazole-5-carboxylic acid

A total of 840 mg of the title compound was obtained as colorless crystals by the procedure of Production Example II-9-c, except from 500 mg of 7-fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid obtained in Production Example II-32-d.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.14-7.36 (15H, m), 7.46 (1H, dd, J = 1.2, 12.4 Hz), 7.55-7.58 (2H, m), 7.85 (1H, dd, J = 2.0, 8.8 Hz), 7.92-7.96 (1H, m), 8.03 (1H, d, J = 1.2, 8.8 Hz), 8.06-8.09 (1H, m), 8.41 (1H, s), 8.56 (1H, d, J = 1.2 Hz).

PRODUCTION EXAMPLE II-37-b

7-Fluoro-3-naphthalen-2-yl-1-trityl-1*H*-indazol-5-ylamine

A total of 320 mg of the title compound was obtained as colorless crystals by the procedure of Production Example II-36-b, except from 870 mg of 7-fluoro-3-naphthalen-2-yl-1-trityl-1*H*-indazole-5-carboxylic acid.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 5.18 (2H, d, J = 8.4 Hz), 6.36 (1H, dd, J = 1.6, 9.6 Hz), 7.11 (1H, d, J = 1.6 Hz), 7.22-7.33 (15H, m), 7.50 (1H, dt, J = 1.2, 6.8 Hz), 7.54 (1H, dt, J = 1.2, 6.8 Hz), 7.80 (1H, dd, J = 1.2, 8.8 Hz), 7.88-7.97 (3H, m), 8.27 (1H, s).

PRODUCTION EXAMPLE II-38-a

(4-Methoxy-3-naphthalen-2-yl-1-trityl-1*H*-indazol-5-yl)-carbamic acid benzyl ester

493 mg of 4-methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid obtained in Production Example II-10-d was dissolved in 10 ml of dimethylformamide. Under ice-cooling and stirring, 136 mg of sodium hydride (content 60%) was

added thereto. After stirring for 15 minutes, 454 mg of triphenylmethyl chloride was added. After stirring at room temperature for 2 hours, the reaction mixture was diluted with saturated aqueous ammonium chloride solution and was extracted with ethyl acetate. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (chloroform:methanol=20:1), to give 728 mg of a trityl derivative as an ocher yellow amorphous substance. The resulting compound was dissolved in 10 ml of toluene, and 0.27 ml of triethylamine and 0.28 ml of diphenylphosphoryl azide were added to the solution at room temperature under stirring. The mixture was stirred at room temperature for 2 hours and at 120°C for further 1.5 hours. 0.67 ml of benzyl alcohol was added thereto, followed by stirring at 120°C for 1.5 hours. After cooling to room temperature, water was added thereto and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane=1:4), to give 466 mg of the title compound as an ocher yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.38 (3H, s), 5.20 (2H, s), 6.29 (1H, d, J = 9.6 Hz), 7.17-7.49 (23H, m), 7.84-7.90 (3H, m), 8.02 (1H, d, J = 7.2 Hz), 8.44 (1H, s).

PRODUCTION EXAMPLE II-38-b

4-Methoxy-3-naphthalen-2-yl-1-trityl-1*H*-indazol-5-ylamine

466 mg of (4-methoxy-3-naphthalen-2-yl-1-trityl-1*H*-indazol-5-yl)-carbamic acid benzyl ester obtained in Production Example II-38-a was dissolved in 20 ml of a 1:1 solvent mixture of ethyl acetate and methanol. 300 mg of 10% palladium-carbon was added and the mixture was subjected to catalytic hydrogenation at room temperature and normal atmospheric pressure. The reaction mixture was filtered through Celite, and the solvent was removed, to give 252 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.37 (3H, s), 6.21 (1H, d, J = 8.8 Hz), 6.81 (1H, d, J = 9.2 Hz), 7.06 (1H, t, J = 7.6 Hz), 7.18-7.61 (17H, m), 7.97-8.01 (3H, m), 8.46 (1H, s).

PRODUCTION EXAMPLE II-39-a

(3-Benzo[*b*]thiophen-2-yl-4-methoxy-1-trityl-1*H*-indazol-5-yl)carbamic acid benzyl ester

548 mg of 3-benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid obtained in Production Example II-12-d was dissolved in 10 ml of dimethylformamide. Under ice-cooling and stirring, 149 mg of sodium hydride (content 60%) was added and the mixture was stirred for 15 minutes. Then, 495 mg of triphenylmethyl chloride was added and the mixture was stirred at room temperature for 2 hours. Then, saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The

resulting organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (chloroform:methanol=20:1), to give 854 mg of a trityl derivative as an ocher yellow amorphous substance. The resulting compound was dissolved in 10 ml of toluene, 0.32 ml of triethylamine and 0.36 ml of diphenylphosphoryl azide were added, followed by stirring at room temperature for 2 hours and at 120°C for 1.5 hours. Then, 0.78 ml of benzyl alcohol was added, followed by stirring at 120°C for 1.5 hours. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane=1:4), to give 939 mg of the title compound as an ocher yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.70 (3H, s), 5.20 (2H, s), 6.23 (1H, d, J = 9.2 Hz), 7.21-7.39 (23H, m), 7.78 (2H, d, J = 8.4 Hz), 8.01 (1H, s).

PRODUCTION EXAMPLE II-39-b

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1-trityl-1*H*-indazol-5-ylamine

A total of 939 mg of (3-benzo[*b*]thiophen-2-yl-4-methoxy-1-trityl-1*H*-indazol-5-yl)-carbamic acid benzyl ester obtained in Production Example II-39-a was dissolved

in 20 ml of a 2:1 solvent mixture of ethyl acetate and methanol. 300 mg of 20% palladium hydroxide-carbon was added thereto, and the mixture was subjected to catalytic hydrogenation at room temperature and at normal atmospheric pressure in the presence of. The reaction mixture was filtrated through Celite, and the solvent was removed, to give 458 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.63 (3H, s), 6.02 (1H, d, J = 8.8 Hz), 6.68 (1H, d, J = 8.8 Hz), 7.00 (1H, t, J = 7.2 Hz), 7.10-7.36 (16H, m), 7.87 (2H, t, J = 8.0 Hz), 8.07 (1H, s).

PRODUCTION EXAMPLE II-40

C-(7-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)methylamine

A total of 260 mg of the title compound was obtained as colorless crystals by the procedure of Production Example II-26, except from 280 mg of 7-fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carbonitrile obtained in Production Example II-32-c.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 3.86 (2H, s), 7.28 (1H, d, J = 12.0 Hz), 7.50-7.60 (2H, m), 7.95 (1H, d, J = 8.4 Hz), 7.98 (1H, s), 8.03 (1H, d, J = 8.4 Hz), 8.10 (1H, d, J = 8.4 Hz), 8.16 (1H, dd, J = 1.6, 8.4 Hz), 8.54 (1H, s).

PRODUCTION EXAMPLE II-41-a

5-Bromo-2-fluoro-4-methoxy-benzaldehyde

8.4 g of 1-bromo-4-fluoro-2-methoxy-benzene obtained in Production Example II-1-a was dissolved in 200 ml of dichloromethane. 21 ml of titanium tetrachloride and 5.6

ml of dichloromethyl methyl ether were added at 0°C in nitrogen atmosphere, followed by stirring at room temperature for 4.5 hours. Then, the reaction mixture was gradually poured onto ice-water, and extracted with diethyl ether for two times. The organic layer was sequentially washed with each one portion of water, saturated aqueous sodium hydrogencarbonate solution and water, dried over magnesium sulfate and the solvent was evaporated, to give 9.44 g of the title compound as white crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.97 (3H, s), 6.67 (1H, d, J = 12.0 Hz), 8.05 (1H, d, J = 7.6 Hz), 10.15 (1H, s)

PRODUCTION EXAMPLE II-41-b

4-Fluoro-5-formyl-2-methoxy-benzonitrile

5.33 g of 5-bromo-2-fluoro-4-methoxy-benzaldehyde was dissolved in 73 ml of 1-methyl-2-pyrrolidone, 2.46 g of copper cyanide was added under stirring at 180°C for 5.5 hours. After cooling to room temperature, water was added to the reaction mixture. The mixture was extracted with ethyl acetate and filtered through Celite. Then, the resulting organic layer was washed with water and brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography, to give 0.983 g of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.03 (3H, s), 6.76 (1H, d, J = 12.0 Hz), 8.14 (1H, d, J = 7.2 Hz), 10.17 (1H, s)

PRODUCTION EXAMPLE II-41-c

6-Methoxy-1*H*-indazole-5-carbonitrile

A total of 0.915 g of the title compound was obtained as pale yellow crystals by the procedure of Production Example II-1-d, except from 0.983 g of 4-fluoro-5-formyl-2-methoxy-benzonitrile.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.99 (3H, s), 7.10 (1H, s), 8.06 (1H, s), 8.15 (1H, s)

PRODUCTION EXAMPLE II-41-d

3-Bromo-6-methoxy-1*H*-indazole-5-carbonitrile

A total of 1.2 g of the title compound was obtained as yellow crystals by the procedure of Production Example II-13-d, except from 0.915 g of 6-methoxy-1*H*-indazole-5-carbonitrile.

^{1}H-NMR (400 MHz, CD_3OD) δ 4.00 (3H, s), 7.10 (1H, s), 7.97 (1H, s)

PRODUCTION EXAMPLE II-41-e

3-Bromo-6-methoxy-1-trityl-1*H*-indazole-5-carbonitrile

A total of 2.41 g of the title compound was obtained as brown crystals by the procedure of Production Example II-9-c, except from 1.2 g of 3-bromo-6-methoxy-1*H*-indazole-5-carbonitrile.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.36 (3H, s), 5.60 (1H, s), 7.14 - 7.17 (5H, m), 7.24 - 7.32 (10H, m), 7.81 (1H, s)

PRODUCTION EXAMPLE II-41-f

6-Methoxy-3-naphthalen-2-yl-1-trityl-1*H*-indazole-5-

carbonitrile

A total of 249 mg of the title compound (a Suzuki coupling product) was obtained as white crystals by the procedure of Production Example II-13-f, except from 600 mg of 3-bromo-6-methoxy-1-trityl-1*H*-indazole-5-carbonitrile and 260 mg of 2-naphthaleneboronic acid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.39 (3H, s), 5.73 (1H, s), 7.14 - 7.33 (16H, m), 7.49 - 7.53 (2H, m), 7.84 - 7.95 (3H,m), 8.28 (1H, s), 8.38 (1H, s)

PRODUCTION EXAMPLE II-41-g

6-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid

A total of 104.3 mg of the title compound was obtained as brown crystals by the procedure of Production Example II-1-e, except from 249 mg of 6-methoxy-3-naphthalen-2-yl-1-trityl-1*H*-indazole-5-carbonitrile.

^{1}H-NMR (400 MHz, CD_3OD) δ 4.02 (3H, s), 7.15 (1H, s), 7.53 - 7.58 (2H, m), 7.91 - 7.94 (1H, m), 8.00 - 8.06 (3H, m), 8.41 (1H, s), 8.66 (1H, s)

ESI-MS: m/z=319 $(M+H)^+$

PRODUCTION EXAMPLE II-42-a

3-Benzo[*b*]thiophen-2-yl-6-methoxy-1-trityl-1*H*-indazole-5-carbonitrile

A total of 292.5 mg of the title compound (a Suzuki coupling product) was obtained as white crystals by the procedure of Production Example II-13-f, except from 600 mg of 3-bromo-6-methoxy-1-trityl-1*H*-indazole-5-carbonitrile

obtained in Production Example II-41-e and 269 mg of 2-benzo[*b*]thiopheneboronic acid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.37 (3H, s), 5.69 (1H, s), 7.14 - 7.89 (20H, m), 8.34 (1H, s)

PRODUCTION EXAMPLE II-42-b

3-Benzo[*b*]thiophen-2-yl-6-methoxy-1*H*-indazole-5-carboxylic acid

A total of 133.6 mg of the title compound was obtained as brown crystals by the procedure of Production Example II-1-e, except from 292.5 mg of 3-benzo[*b*]thiophen-2-yl-6-methoxy-1-trityl-1*H*-indazole-5-carbonitrile.

^{1}H-NMR (400 MHz, CD_3OD) δ 4.00 (3H, s), 7.12 (1H, s), 7.34-7.40 (2H, m), 7.88 - 7.92 (2H, m), 7.95 (1H, s), 8.69 (1H, s)

ESI-MS: m/z=325 $(M+H)^+$

PRODUCTION EXAMPLE II-43-a

3-Benzo[*b*]furan-2-yl-4-fluoro-1-trityl-1*H*-5-indazolecarboxylic acid

A total of 146 mg of the title compound was obtained as bright yellow crystals by the hydrolysis procedure of Production Example II-33-a, except from 152 mg of 3-benzo[*b*]furan-2-yl-4-fluoro-1-trityl-1*H*-5-indazolecarboxylic acid methyl ester obtained in the coupling reaction of Production Example II-15-a.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 6.36 (1H, d J = 8.8 Hz), 7.18 - 7.40 (17H, m), 7.44 (1H, s), 7.56 (1H, dd, J = 7.2, 8.8 Hz), 7.63 (1H, d, J = 8.0Hz), 7.74 (1H, d, J = 7.6 Hz), 13.19 (1H, s).

PRODUCTION EXAMPLE II-43-b

{3-Benzo[*b*]furan-2-yl-4-fluoro-1-trityl-1*H*-indazol-5-yl}carbamic acid benzyl ester

A total of 26 mg of the title compound was obtained as a white amorphous powder by the procedure of Production Example II-19-b, except from 144 mg of 3-benzo[*b*]furan-2-yl-4-fluoro-1-trityl-1*H*-5-indazolecarboxylic acid obtained in Production Example II-43-a.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 5.12 (2H, s), 6.28 (1H, d, J = 9.2 Hz), 7.16 - 7.44 (24H, m), 7.60 (1H, d, J = 8.4 Hz), 7.73 (1H, d, J = 8.0 Hz), 9.40 (1H, s).

PRODUCTION EXAMPLE II-43-c

3-Benzo[*b*]furan-2-yl-4-fluoro-1-trityl-1*H*-indazol-5-ylamine

A total of 24 mg of the title compound was obtained as a pale yellow viscous oily substance by the procedure of Production Example II-19-c, except from 26 mg of {3-benzo[*b*]furan-2-yl-4-fluoro-1-trityl-1*H*-indazol-5-yl}carbamic acid benzyl ester obtained in Production Example II-43-b.

^{1}H-NMR (400MHz, DMSO-D_6) δ 4.99 (2H, s), 6.06 (1H, d, J = 8.8 Hz), 6.69 (1H, t, J = 8.8 Hz), 7.14 - 7.41 (18H, m), 7.57 (1H, d, J = 8.0 Hz), 7.69 (1H, d, J = 7.6 Hz)

Typical synthesis processes for the compounds according to the examples will be illustrated below.

Synthesis Process II-A

Each of the carboxylic acids produced in Production

Examples II was dissolved in dimethylformamide and was pipetted into test tubes. To each test tube were sequentially added 1.2 equivalents of a 1 M solution of various of amines in dimethylformamide, 1.2 equivalents of a 1 M solution of 1-hydroxybenzotriazole monohydrate in dimethylformamide, 4 equivalents of diisopropylethylamine, and 2 equivalents of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (i.e., WSC.HCl), each of which had been previously prepared. The mixture was stirred at room temperature overnight. The reaction mixture was purified and separated by LC-MS (developing solvent; acetonitrile solution containing 0.1% trifluoroacetic acid: aqueous solution containing 0.1% trifluoroacetic acid = 20:80 to 80:20, 10 minute-cycle, flow rate; 30 ml/min, column; YMC Combiprep ODS-AM, 20 mmΦ x 50 mm (Long)), to give the compounds according to Examples.

Synthesis Process II-B

Each of the amines produced in Production Examples II was dissolved in dimethylformamide and was pipetted into test tubes. To each test tube were sequentially added 1.2 equivalents of a 1 M solution of any of carboxylic acids in dimethylformamide, 1.2 equivalents of a 1 M solution of 1-hydroxybenzotriazole monohydrate in dimethylformamide, 4 equivalents of diisopropylethylamine and 2 equivalents of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

(i.e., WSC.HCl), each of which had been previously prepared. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and was extracted with ethyl acetate. The extract was air-dried by blowing nitrogen gas to remove the solvent, and the residue was treated with a 1:5 mixture solution of trifluoroacetic acid and dichloromethane, and the mixture was stirred at room temperature overnight. The reaction mixture was air-dried by blowing nitrogen gas to remove the solvent, and the residue was dissolved in dimethylformamide. Each was purified and separated by LC-MS under the same conditions as in Synthesis Process II-A and thereby yielded the compounds according to Examples.

Synthesis Process II-C

Each of the amines produced in Production Examples II was dissolved in dimethylformamide and was pipetted into test tubes. To each test tube were sequentially added 1.2 equivalents of a 1 M solution of any of carboxylic acids in dimethylformamide, 1.2 equivalents of a 1 M solution of 1-hydroxybenzotriazole monohydrate in dimethylformamide, 4 equivalents of diisopropylethylamine and 2 equivalents of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (i.e., WSC.HCl), each of which had been previously prepared. The mixture was stirred at room temperature overnight. Each mixture was purified and separated by LC-MS under the same conditions as in Synthesis Process II-A, to give the

compounds according to Examples.

Synthesis Process II-D

Each of the amines produced in Production Examples II was dissolved in dichloromethane and was pipetted into test tubes (1 ml each). To each test tube were sequentially added 3 equivalents of triethylamine and 2 equivalents of any of sulfonyl chlorides, and the mixture was stirred at room temperature overnight. The reaction mixture was treated with 0.2 ml of trifluoroacetic acid under stirring at room temperature overnight. The reaction mixture was air-dried by blowing nitrogen gas, and the residue was dissolved in dimethylformamide. Each was purified and separated by LC-MS under the same conditions as in Synthesis Process II-A, to give the compounds according to Examples.

Synthesis Process II-E

Each of the amines produced in Production Examples II was dissolved in 1 ml of dichloromethane. Each solution was treated with 0.2 ml of trifluoroacetic acid under stirring at room temperature overnight. The reaction mixture was air-dried by blowing nitrogen gas, and the residue was dissolved in dimethylformamide. Each was purified and separated by LC-MS under the same conditions as in Synthesis Process II-A, to give the compounds according to Examples.

The compounds according to Examples II-1 to II-152

were synthesized by Synthesis Process II-A using the carboxylic acids produced in Production Examples II-1 to II-17.

EXAMPLE II-1

3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 366 MH^+

EXAMPLE II-2

3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazole-5-carboxylic acid (2-acetylamino-ethyl)-amide

MS (ESI)m/z 371 MH^-

EXAMPLE II-3

3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazole-5-carboxylic acid [(1S)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 372 MH^-

EXAMPLE II-4

3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide

MS (ESI)m/z 377 MH^+

EXAMPLE II-5

3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 366 MH^+

EXAMPLE II-6

3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazole-5-carboxylic acid (2-acetylamino-ethyl)-amide

MS (ESI)m/z 371 MH^+

EXAMPLE II-7

3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazole-5-carboxylic acid [(1S)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 372 MH^+

EXAMPLE II-8

3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide

MS (ESI)m/z 377 MH^+

EXAMPLE II-9

3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 326 MH^+

EXAMPLE II-10

3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 326 MH^+

EXAMPLE II-11

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 314 MH^+

EXAMPLE II-12

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazcle-5-carboxylic acid (2-acetylamino-ethyl)-amide

MS (ESI)m/z 359 MH^-

EXAMPLE II-13

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid (2-dimethylamino-ethyl)-amide

MS (ESI)m/z 345 MH^+

EXAMPLE II-14

3-(3-Fluoro-phenyl)-6-hydroxy-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 312 MH^+

EXAMPLE II-15

3-(3-Fluoro-phenyl)-6-hydroxy-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 352 MH^+

EXAMPLE II-16

3-(3-Fluoro-phenyl)-6-hydroxy-1*H*-indazole-5-carboxylic acid (2-acetylamino-ethyl)-amide

MS (ESI)m/z 357 MH^+

EXAMPLE II-17

3-(3-Fluoro-phenyl)-6-hydroxy-1*H*-indazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide

MS (ESI)m/z 363 MH^+

EXAMPLE II-18

3-(3-Fluoro-phenyl)-6-hydroxy-1*H*-indazole-5-carboxylic acid (2-dimethylamino-ethyl)-amide

MS (ESI)m/z 343 MH^+

EXAMPLE II-19

3-(3-Fluoro-phenyl)-6-hydroxy-1*H*-indazole-5-carboxylic acid (1*H*-imidazol-4-ylmethyl)-amide

MS (ESI)m/z 352 MH^-

EXAMPLE II-20

6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 354 MH^+

EXAMPLE II-21

6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid (2-acetylamino-ethyl)-amide

MS (ESI)m/z 359 MH^+

EXAMPLE II-22

6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide

MS (ESI)m/z 365 MH^+

EXAMPLE II-23

6-Fluoro-3-(3-fluorc-phenyl)-1*H*-indazole-5-carboxylic acid (2-dimethylamino-ethyl)-amide

MS (ESI)m/z 345 MH^+

EXAMPLE II-24

6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid (1*H*-imidazol-4-ylmethyl)-amide

MS (ESI)m/z 354 MH^+

EXAMPLE II-25

6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 314 MH^+

EXAMPLE II-26

3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazole-5-carboxylic acid 3-methoxy-benzylamide

MS (ESI)m/z 406 MH^+

EXAMPLE II-27

6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid 3-methoxy-benzylamide

MS (ESI)m/z 394 MH^-

EXAMPLE II-28

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid 3-methoxy-benzylamide

MS (ESI)m/z 390 MH^+

EXAMPLE II-29

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid 3-methoxy-benzylamide

MS (ESI)m/z 394 MH^+

EXAMPLE II-30

3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide

MS (ESI)m/z 411 MH^+

EXAMPLE II-31

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide

MS (ESI)m/z 395 MH^+

EXAMPLE II-32

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide

MS (ESI)m/z 399 MH^+

EXAMPLE II-33

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid (2-thiophen-2-yl-ethyl)-amide

MS (ESI)m/z 380 MH^+

EXAMPLE II-34

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid (2-thiophen-2-yl-ethyl)-amide

MS (ESI)m/z 384 MH^+

EXAMPLE II-35

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid (tetrahydrofuran-2-ylmethyl)-amide

MS (ESI)m/z 358 MH^+

EXAMPLE II-36

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid (2-ethoxy-ethyl)-amide

MS (ESI)m/z 346 MH^+

EXAMPLE II-37

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid (2-ethoxy-ethyl)-amide

MS (ESI)m/z 342 MH^+

EXAMPLE II-38

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid cyclopropylmethyl-amide

MS (ESI)m/z 324 MH^+

EXAMPLE II-39

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid (2-methylsulfanyl-ethyl)-amide

MS (ESI)m/z 344 MH^+

EXAMPLE II-40

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid (2-methylsulfanyl-ethyl)-amide

MS (ESI)m/z 348 MH^+

EXAMPLE II-41

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoyl-ethyl]-amide

MS (ESI)m/z 341 MH^+

EXAMPLE II-42

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoyl-ethyl]-amide

MS (ESI)m/z 345 MH^+

EXAMPLE II-43

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid [(1*S*)-2-hydroxy-1-phenyl-ethyl]-amide

MS (ESI)m/z 390 MH^+

EXAMPLE II-44

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid [(1*S*)-2-hydroxy-1-phenyl-ethyl]-amide

MS (ESI)m/z 394 MH^+

EXAMPLE II-45

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid (2-thiazol-2-yl-ethyl)-amide

MS (ESI)m/z 381 MH+

EXAMPLE II-46

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid (2-thiazol-2-yl-ethyl)-amide

MS (ESI)m/z 385 MH+

EXAMPLE II-47

3-(3-Fluoro-phenyl)-6-methyl-1*H*-indazole-5-carboxylic acid [(3*R*)-2-oxo-tetrahydrofuran-3-yl]-amide

MS (ESI)m/z 354 MH+

EXAMPLE II-48

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazole-5-carboxylic acid [(3*R*)-2-oxo-tetrahydrofuran-3-yl]-amide

MS (ESI)m/z 358 MH+

EXAMPLE II-49

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 326 MH+

EXAMPLE II-50

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carboxylic acid (2-methylsulfanylethyl)amide

MS (ESI)m/z 360 MH+

EXAMPLE II-51

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]amide

MS (ESI)m/z 372 MH+

EXAMPLE II-52

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carboxylic acid [tetrahydrofuran-(2*S*)-2-ylmethyl]amide

MS (ESI)m/z 370 MH^+

EXAMPLE II-53

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carboxylic acid [tetrahydrofuran-(2*R*)-2-ylmethyl]amide

MS (ESI)m/z 370 MH^+

EXAMPLE II-54

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)amide

MS (ESI)m/z 366 MH^+

EXAMPLE II-55

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carboxylic acid (5-methylfuran-2-ylmethyl)amide

MS (ESI)m/z 380 MH^+

EXAMPLE II-56

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carboxylic acid (thiophen-2-ylmethyl)amide

MS (ESI)m/z 382 MH^+

EXAMPLE II-57

3-(3-Fluorophenyl)-7-methoxy-1*H*-indazole-5-carboxylic acid (benzo[*b*]furan-2-ylmethyl)amide

MS (ESI)m/z 416 MH^+

EXAMPLE II-58

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 310 MH^+

EXAMPLE II-59

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carboxylic acid (2-methylsulfanylethyl)amide

MS (ESI)m/z 344 MH^+

EXAMPLE II-60

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]amide

MS (ESI)m/z 356 MH^+

EXAMPLE II-61

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carboxylic acid [tetrahydrofuran-(2*S*)-2-ylmethyl]amide

MS (ESI)m/z 354 MH^+

EXAMPLE II-62

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carboxylic acid [tetrahydrofuran-(2*R*)-2-ylmethyl]amide

MS (ESI)m/z 354 MH^+

EXAMPLE II-63

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)amide

MS (ESI)m/z 350 MH^+

EXAMPLE II-64

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carboxylic acid (5-methylfuran-2-ylmethyl)amide

MS (ESI)m/z 364 MH^+

EXAMPLE II-65

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carboxylic acid (thiophen-2-ylmethyl)amide

MS (ESI)m/z 366 MH^+

EXAMPLE II-66

3-(3-Fluorophenyl)-7-methyl-1*H*-indazole-5-carboxylic acid (benzo[*b*]furan-2-ylmethyl)amide

MS (ESI)m/z 400 MH^+

EXAMPLE II-67

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (2-thiophen-2-yl-ethyl)-amide

MS (ESI)m/z 428 MH^+

EXAMPLE II-68

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (2-methylsulfanyl-ethyl)-amide

MS (ESI)m/z 392 MH^+

EXAMPLE II-69

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoyl-ethyl]-amide

MS (ESI)m/z 389 MH^+

EXAMPLE II-70

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-2-hydroxy-1-phenyl-ethyl]-amide

MS (ESI)m/z 438 MH^+

EXAMPLE II-71

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (2-thiazol-2-yl-ethyl)-amide

MS (ESI)m/z 429 MH^+

EXAMPLE II-72

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(3*R*)-2-oxo-tetrahydrofuran-3-yl]-amide

MS (ESI)m/z 402 MH^+

EXAMPLE II-73

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (tetrahydrofuran-2-ylmethyl)-amide

MS (ESI)m/z 402 M^+

EXAMPLE II-74

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (2-ethoxy-ethyl)-amide

MS (ESI)m/z 390 MH^+

EXAMPLE II-75

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid cyclopropylmethyl-amide

MS (ESI)m/z 372 MH^+

EXAMPLE II-76

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 398 MH^+

EXAMPLE II-77

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (5-methyl-furan-2-ylmethyl)-amide

MS (ESI)m/z 412 MH^+

EXAMPLE II-78

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid cyclopropyl-amide

MS (ESI)m/z 358 MH^+

EXAMPLE II-79

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid 3-methoxy-benzylamide

MS (ESI)m/z 438 MH^+

EXAMPLE II-80

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide

MS (ESI)m/z 443 MH^+

EXAMPLE II-81

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 404 MH^+

EXAMPLE II-82

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (furan-3-ylmethyl)-amide

MS (ESI)m/z 398 MH^+

EXAMPLE II-83

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide

MS (ESI)m/z 409 MH^+

EXAMPLE II-84

4-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (thiophen-2-ylmethyl)-amide

MS (ESI)m/z 414 MH^+

EXAMPLE II-85

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (2-thiophen-2-yl-ethyl)-amide

MS (ESI)m/z 418 MH^+

EXAMPLE II-86

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (2-methylsulfanyl-ethyl)-amide

MS (ESI)m/z 382 MH^+

EXAMPLE II-87

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoyl-ethyl]-amide

MS (ESI)m/z 379 MH^+

EXAMPLE II-88

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid [(1*S*)-2-hydroxy-1-phenyl-ethyl]-amide

MS (ESI)m/z 428 MH^+

EXAMPLE II-89

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (2-thiazol-2-yl-ethyl)-amide

MS (ESI)m/z 419 MH^+

EXAMPLE II-90

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid [(3*R*)-2-oxo-tetrahydrofuran-3-yl]-amide

MS (ESI)m/z 392 MH^+

EXAMPLE II-91

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (tetrahydrofuran-2-ylmethyl)-amide

MS (ESI)m/z 392 M^+

EXAMPLE II-92

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (2-ethoxy-ethyl)-amide

MS (ESI)m/z 380 MH^+

EXAMPLE II-93

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid cyclopropylmethyl-amide

MS (ESI)m/z 362 MH^+

EXAMPLE II-94

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 388 MH^+

EXAMPLE II-95

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (5-methyl-furan-2-ylmethyl)-amide

MS (ESI)m/z 402 MH^+

EXAMPLE II-96

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 348 MH^+

EXAMPLE II-97

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid 3-methoxy-benzylamide

MS (ESI)m/z 428 MH^-

EXAMPLE II-98

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide

MS (ESI)m/z 433 MH^+

EXAMPLE II-99

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 394 MH^+

EXAMPLE II-100

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (furan-3-ylmethyl)-amide

MS (ESI)m/z 388 MH^+

EXAMPLE II-101

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide

MS (ESI)m/z 399 MH^+

EXAMPLE II-102

3-Benzo[*b*]furan-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (thiophen-2-ylmethyl)-amide

MS (ESI)m/z 404 MH^+

EXAMPLE II-103

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (2-thiophen-2-yl-ethyl)-amide

MS (ESI)m/z 434 MH^+

EXAMPLE II-104

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (2-methylsulfanyl-ethyl)-amide

MS (ESI)m/z 398 MH^+

EXAMPLE II-105

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoyl-ethyl]-amide

MS (ESI)m/z 395 MH^+

EXAMPLE II-106

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid [(1*S*)-2-hydroxy-1-phenyl-ethyl]-amide

MS (ESI)m/z 444 MH^+

EXAMPLE II-107

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (2-thiazol-2-yl-ethyl)-amide

MS (ESI)m/z 435 MH^+

EXAMPLE II-108

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid [(3*R*)-2-oxo-tetrahydrofuran-3-yl]-amide

MS (ESI)m/z 408 MH^+

EXAMPLE II-109

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (tetrahydrofuran-2-ylmethyl)-amide

MS (ESI)m/z 408 M^+

EXAMPLE II-110

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (2-ethoxy-ethyl)-amide

MS (ESI)m/z 396 MH^+

EXAMPLE II-111

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid cyclopropylmethyl-amide

MS (ESI)m/z 378 MH^+

EXAMPLE II-112

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 404 MH^+

EXAMPLE II-113

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (5-methyl-furan-2-ylmethyl)-amide

MS (ESI)m/z 418 MH^+

EXAMPLE II-114

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 364 MH^+

EXAMPLE II-115

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid 3-methoxy-benzylamide

MS (ESI)m/z 444 MH^+

EXAMPLE II-116

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide

MS (ESI)m/z 449 MH^+

EXAMPLE II-117

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 410 MH^+

EXAMPLE II-118

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (furan-3-ylmethyl)-amide

MS (ESI)m/z 404 MH^+

EXAMPLE II-119

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide

MS (ESI)m/z 415 MH^+

EXAMPLE II-120

3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazole-5-carboxylic acid (thiophen-2-ylmethyl)-amide

MS (ESI)m/z 420 MH^+

EXAMPLE II-121

3-Benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid cyclopropanamide

MS (ESI)m/z 352 MH^+

EXAMPLE II-122

3-Benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 392 MH^+

EXAMPLE II-123

3-Benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 398 MH^+

EXAMPLE II-124

3-Benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid (2-acetylamino-ethyl)-amide

MS (ESI)m/z 397 MH^+

EXAMPLE II-125

3-Benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid (2-thiophen-2-yl-ethyl)-amide

MS (ESI)m/z 422 MH^+

EXAMPLE II-126

3-Benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoyl-ethyl]]-amide

MS (ESI)m/z 765 $2MH^+$

EXAMPLE II-127

4-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid cyclopropanamide

MS (ESI)m/z 346 MH^+

EXAMPLE II-128

4-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 386 MH^+

EXAMPLE II-129

4-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 392 MH^+

EXAMPLE II-130

4-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (2-acetylamino-ethyl)-amide

MS (ESI)m/z 391 MH^+

EXAMPLE II-131

4-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (2-thiophen-2-yl-ethyl)-amide

MS (ESI)m/z 416 MH^+

EXAMPLE II-132

4-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoyl-ethyl]-amide

MS (ESI)m/z 753 $2MH^+$

EXAMPLE II-133

3-Benzo[*b*]furan-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid cyclopropanamide

MS (ESI)m/z 336 MH^+

EXAMPLE II-134

3-Benzo[*b*]furan-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 376 MH^+

EXAMPLE II-135

3-Benzo[*b*]furan-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 382 MH^+

EXAMPLE II-136

3-Benzo[*b*]furan-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid (2-acetylamino-ethyl)-amide

MS (ESI)m/z 381 MH$^+$

EXAMPLE II-137

3-Benzo[*b*]furan-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid (2-thiophen-2-yl-ethyl)-amide

MS (ESI)m/z 406 MH$^+$

EXAMPLE II-138

3-Benzo[*b*]furan-2-yl-4-fluoro-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoyl-ethyl]-amide

MS (ESI)m/z 733 2MH$^+$

EXAMPLE II-139

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 352 MH$^+$

EXAMPLE II-140

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 392 MH$^+$

EXAMPLE II-141

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carboxylic acid [(2*S*)-tetrahydrofuran-2-ylmethyl]-amide

MS (ESI)m/z 396 MH$^+$

EXAMPLE II-142

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carboxylic acid [(2*R*)-tetrahydrofuran-2-ylmethyl]-amide

MS (ESI)m/z 396 MH$^+$

EXAMPLE II-143

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide

MS (ESI)m/z 403 MH^+

EXAMPLE II-144

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 398 MH^-

EXAMPLE II-145

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazole-5-carboxylic acid [3-(2-oxopyrrolidin-1-yl)propyl]-amide

MS (ESI)m/z 437 MH^+

EXAMPLE II-146

6-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 346 MH^+

EXAMPLE II-147

6-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 386 MH^-

EXAMPLE II-148

6-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(2*S*)-tetrahydrofuran-2-ylmethyl]-amide

MS (ESI)m/z 390 MH^+

EXAMPLE II-149

6-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(2*R*)-tetrahydrofuran-2-ylmethyl]-amide

MS (ESI)m/z 390 MH^+

EXAMPLE II-150

6-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide

MS (ESI)m/z 397 MH^+

EXAMPLE II-151

6-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 392 MH^+

EXAMPLE II-152

6-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [3-(2-oxopyrrolidin-1-yl)propyl]amide

MS (ESI)m/z 431 MH^+

The compounds according to Examples II-153 to II-197 were synthesized by Synthesis Process II-B using the amines produced in Production Examples II-18 through II-25.

EXAMPLE II-153

Cyclopropanecarboxylic acid {3-(3-fluoro-phenyl)-4-methoxy-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 326 MH^+

EXAMPLE II-154

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid {3-(3-fluoro-phenyl)-4-methoxy-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 369 MH^+

EXAMPLE II-155

(2*R*)-5-Oxo-pyrrolidine-2-carboxylic acid {3-(3-fluoro-

phenyl)-4-methoxy-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 369 MH^+

EXAMPLE II-156

Pyridin-3-yl-acetic acid {3-(3-fluoro-phenyl)-4-methoxy-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 377 MH^+

EXAMPLE II-157

Cyclopropanecarboxylic acid {4-bromo-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 376, 378 MH^+

EXAMPLE II-158

Pyridin-3-yl-acetic acid {4-bromo-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 425, 427 MH^+

EXAMPLE II-159

Cyclopropanecarboxylic acid {4-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 314 MH^+

EXAMPLE II-160

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid {4-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 357 MH^-

EXAMPLE II-161

(2*R*)-5-Oxo-pyrrolidine-2-carboxylic acid {4-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 357 MH^+

EXAMPLE II-162

3-Dimethylamino-N-[4-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl]-propionamide

MS (ESI)m/z 344 MH^+

EXAMPLE II-163

Cyclopropanecarboxylic acid [6-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl]-amide

MS (ESI)m/z 314 MH^+

EXAMPLE II-164

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid [6-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl]-amide

MS (ESI)m/z 357 MH^+

EXAMPLE II-165

(2*R*)-5-Oxo-pyrrolidine-2-carboxylic acid [6-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl]-amide

MS (ESI)m/z 357 MH^+

EXAMPLE II-166

Pyridin-3-yl-acetic acid [6-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl]-amide

MS (ESI)m/z 365 MH^+

EXAMPLE II-167

3-Dimethylamino-N-[6-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl]-propionamide

MS (ESI)m/z 345 MH^-

EXAMPLE II-168

Cyclopropanecarboxylic acid [3-(3-fluoro-phenyl)-6-methoxy-

1*H*-indazol-5-yl}-amide

MS (ESI)m/z 326 MH^+

EXAMPLE II-169

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid {3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 369 MH^+

EXAMPLE II-170

(2*R*)-5-Oxo-pyrrolidine-2-carboxylic acid {3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 369 MH^+

EXAMPLE II-171

Pyridin-3-yl-acetic acid {3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 377 MH^+

EXAMPLE II-172

3-Dimethylamino-N-{3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl}-propionamide

MS (ESI)m/z 357 MH^-

EXAMPLE II-173

N-{3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl}-2-thiophen-2-yl-acetamide

MS (ESI)m/z 382 MH^+

EXAMPLE II-174

Furan-2-carboxylic acid {3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl}-amide

MS (ESI)m/z 352 MH^+

333

EXAMPLE II-175

N-{3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl}-3-methoxy-propionamide

MS (ESI)m/z 344 MH^+

EXAMPLE II-176

N-[3-(3-Fluorophenyl)-7-methyl-1*H*-indazol-5-yl]acetamide

MS (ESI)m/z 284 MH^+

EXAMPLE II-177

Cyclopropanecarboxylic acid [3-(3-fluorophenyl)-7-methyl-1*H*-indazol-5-yl]amide

MS (ESI)m/z 310 MH^+

EXAMPLE II-178

(2*R*)-5-Oxo-pyrrolidine-2-carboxylic acid [3-(3-fluorophenyl)-7-methyl-1*H*-indazol-5-yl]amide

MS (ESI)m/z 353 MH^+

EXAMPLE II-179

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid [3-(3-fluorophenyl)-7-methyl-1*H*-indazol-5-yl]amide

MS (ESI)m/z 353 MH^+

EXAMPLE II-180

Tetrahydrofuran-3-carboxylic acid [3-(3-fluorophenyl)-7-methyl-1*H*-indazol-5-yl]amide

MS (ESI)m/z 340 MH^+

EXAMPLE II-181

Tetrahydrofuran-2-carboxylic acid [3-(3-fluorophenyl)-7-methyl-1*H*-indazol-5-yl]amide

MS (ESI)m/z 340 MH^+

EXAMPLE II-182

N-[3-(3-Fluorophenyl)-7-methyl-1*H*-indazol-5-yl]-2-thiophen-2-yl-acetamide

MS (ESI)m/z 366 MH^+

EXAMPLE II-183

N-[3-(3-Fluorophenyl)-7-methyl-1*H*-indazol-5-yl]-2-thiophen-3-yl-acetamide

MS (ESI)m/z 366 MH^+

EXAMPLE II-184

Cyclopropanecarboxylic acid (6-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 346 MH^+

EXAMPLE II-185

N-(6-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-acetamide

MS (ESI)m/z 320 MH^+

EXAMPLE II-186

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid (6-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 389 MH^+

EXAMPLE II-187

(2*R*)-5-Oxo-pyrrolidine-2-carboxylic acid (6-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 389 MH^+

EXAMPLE II-188

Pyridin-3-yl-acetic acid (6-fluoro-3-naphthalen-2-yl-1*H*-

indazol-5-yl)-amide

MS (ESI)m/z 397 MH^+

EXAMPLE II-189

N-(6-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-2-thiophen-2-yl-acetamide

MS (ESI)m/z 402 MH^-

EXAMPLE II-190

Furan-2-carboxylic acid (6-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 372 MH^-

EXAMPLE II-191

N-(6-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-3-methoxy-propionamide

MS (ESI)m/z 364 MH^+

EXAMPLE II-192

Cyclopropanecarboxylic acid (3-benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 352 MH^+

EXAMPLE II-193

N-(3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-yl)-acetamide

MS (ESI)m/z 326 MH^+

EXAMPLE II-194

(2*R*)-5-Oxo-pyrrolidine-2-carboxylic acid (3-benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 395 MH^+

EXAMPLE II-195

N-(3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-yl)-2-thiophen-2-yl-acetamide

MS (ESI)m/z 408 MH^+

EXAMPLE II-196

Furan-2-carboxylic acid (3-benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 378 MH^-

EXAMPLE II-197

N-(3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-yl)-3-methoxy-propionamide

MS (ESI)m/z 370 MH^+

The compounds according to Examples II-198 to II-211 were synthesized by Synthesis Process II-C using the amines produced in Production Examples II-26 through II-30.

EXAMPLE II-198

N-{3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazol-5-ylmethyl}-3-methoxy-benzamide

MS (ESI)m/z 406 MH^+

EXAMPLE II-199

N-{6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-ylmethyl}-3-methoxy-benzamide

^{1}H-NMR(400MHz, CD_3OD) δ 3.83 (3H, s), 4.73 (2H, d, J = 6.0 Hz), 7.06 - 7.18 (2H, m), 7.29 (1H, d, J = 10.6 Hz), 7.33 - 7.76 (6H, m), 8.05 (1H, d, J = 7.2 Hz), 8.99 (1H, brs)

EXAMPLE II-200

N-{3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazol-5-ylmethyl}-3-methoxy-nicotinamide

MS (ESI)m/z 407 MH^+

EXAMPLE II-201

N-{3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazol-5-ylmethyl}-nicotinamide

MS (ESI)m/z 377 MH^+

EXAMPLE II-202

3-Cyano-N-{3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazol-5-ylmethyl}-benzamide

MS (ESI)m/z 401 MH^+

EXAMPLE II-203

3-Fluoro-N-{3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazol-5-ylmethyl}-benzamide

MS (ESI)m/z 394 MH^-

EXAMPLE II-204

N-{6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-ylmethyl}-3-methoxy-nicotinamide

MS (ESI)m/z 395 MH^-

EXAMPLE II-205

N-{6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-ylmethyl}-nicotinamide

MS (ESI)m/z 365 MH^-

EXAMPLE II-206

3-Cyano-N-{6-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-ylmethyl}-benzamide

MS (ESI)m/z 389 MH^+

EXAMPLE II-207

3-Fluoro-N-{6-fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-ylmethyl}-benzamide

MS (ESI)m/z 382 MH^+

EXAMPLE II-208

N-{6-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-ylmethyl}-3-methoxy-benzamide

MS (ESI)m/z 426 MH^+

EXAMPLE II-209

N-{6-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-ylmethyl}-2-methoxy-benzamide

MS (ESI)m/z 426 MH^+

EXAMPLE II-210

N-(3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-ylmethyl)-3-methoxy-benzamide

MS (ESI)m/z 432 MH^+

EXAMPLE II-211

N-(3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-ylmethyl)-2-methoxy-benzamide

MS (ESI)m/z 432 MH^+

The compounds according to Examples II-212 to II-218 were synthesized by Synthesis Process II-D using the amines produced in Production Examples II-18, II-19, II-22, II-23, II-24, II-26, and II-28, respectively.

EXAMPLE II-212

N-{3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazol-5-yl}-methanesulfonamide

MS (ESI)m/z 336 MH^+

EXAMPLE II-213

N-{4-Fluoro-3-(3-Fluoro-phenyl)-1*H*-indazol-5-yl)-methanesulfonamide

MS (ESI)m/z 324 MH^+

EXAMPLE II-214

N-{3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl}-methanesulfonamide

MS (ESI)m/z 336 MH^+

EXAMPLE II-215

N-[3-(3-Fluorophenyl)-7-methyl-1*H*-indazol-5-yl]methanesulfonamide

MS (ESI)m/z 320 MH^+

EXAMPLE II-216

N-{3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazol-5-ylmethyl}-3-methoxy-benzenesulfonamide

MS (ESI)m/z 442 MH^-

EXAMPLE II-217

N-{6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-ylmethyl}-3-methoxy-benzenesulfonamide

MS (ESI)m/z 430 MH^+

EXAMPLE II-218

N-(3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-yl)-methanesulfonamide

MS (ESI)m/z 362 MH^+

The compounds according to Examples II-219 to II-225 were synthesized by Synthesis Process II-E using the amines produced in Production Examples II-18 through II-25, respectively.

EXAMPLE II-219

3-(3-Fluoro-phenyl)-4-methoxy-1*H*-indazol-5-yl-amine

MS (ESI)m/z 258 MH^+

EXAMPLE II-220

4-Bromo-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl-amine

MS (ESI)m/z 306, 308 MH^+

EXAMPLE II-221

4-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl-amine

MS (ESI)m/z 246 MH^+

EXAMPLE II-222

6-Fluoro-3-(3-fluoro-phenyl)-1*H*-indazol-5-yl-amine

MS (ESI)m/z 246 MH^+

EXAMPLE II-223

3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl-amine

MS (ESI)m/z 258 MH^+

EXAMPLE II-224

6-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-ylamine

MS (ESI)m/z 278 MH^+

EXAMPLE II-225

3-Benzo[*b*]thiophen-2-yl-6-fluoro-1*H*-indazol-5-ylamine

MS (ESI)m/z 284 MH^+

EXAMPLE II-226-a

Cyclopropanecarboxylic acid {4-bromo-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazol-5-yl}-amide

A total of 513 mg of 4-bromo-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazol-5-yl-amine obtained in Production Example II-21 was dissolved in 19 ml of tetrahydrofuran. Under ice-cooling and stirring, 0.261 ml of triethylamine and 0.089 ml of cyclopropanecarbonyl chloride were added, and the mixture was stirred at room temperature for 90 minutes. Water was added to the reaction mixture, followed by extracting with ethyl acetate. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:2), to give 471 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 - 0.90 (2H, m), 1.02 - 1.09 (2H, m), 1.53 - 1.60 (1H, m), 6.45 (1H, d, J=9.2 Hz), 7.05 - 7.13 (1H, m), 7.19 - 7.93 (20H, m)

EXAMPLE II-226-b

5-(Cyclopropanecarbonyl-amide)-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazole-4-carboxylic acid

A total of 17.8 mg of the title compound was obtained by the procedure of Production Example II-2-d, except from 144 mg of cyclopropanecarboxylic acid {4-bromo-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazol-5-yl}amide obtained in Example II-226-a.

^{1}H-NMR (400 MHz, CD_3OD) δ 0.72 – 1.71 (5H, m), 6.48 (1H, d, J = 9.2 Hz), 6.98 – 7.05 (1H, m), 7.20 – 7.50 (19H, m)

EXAMPLE II-226-c

5-(Cyclopropanecarbonyl-amide)-3-(3-fluoro-phenyl)-1*H*-indazole-4-carboxylic acid

178 mg of 5-(cyclopropanecarbonyl-amide)-3-(3-fluoro-phenyl)-1-trityl-1*H*-indazole-4-carboxylic acid obtained in Example II-226-b was dissolved in 2 ml of tetrahydrofuran and 2 ml of dichloromethane. 0.5 ml of trifluoroacetic acid was added, followed by stirring at room temperature for 16 hours. Water was added to the reaction mixture, followed by extracting with ethyl acetate. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate), to give 96.9 mg of the title compound as pale pink crystals.

^{1}H-NMR (400 MHz, CD_3OD) δ 0.83 – 1.00 (4H, m), 1.73-1.83 (1H, m), 7.10-7.17 (1H, m), 7.23 – 7.28 (1H, m), 7.31 – 7.36 (1H, m), 7.44 (1H, dt, J = 6.0, 8.0 Hz), 7.68 (1H, d, J = 9.2 Hz), 7.87 (1H, d, J = 9.2 Hz)

EXAMPLE II-227

N-{3-(3-Fluoro-phenyl)-6-methoxy-1*H*-indazol-5-ylmethyl}-3-methoxy-benzamide

A total of 25.6 mg of C-{3-(3-fluoro-phenyl)-6-methoxy-1*H*-indazol-5-yl}-methylamine obtained in Production Example II-26 was dissolved in 1.9 ml of dimethylformamide,

15.3 mg of 1-hydroxybenzotriazole, 0.066 ml of diisopropylethylamine and 14.4 mg of 3-methoxybenzoic acid were added thereto, and 27.2 mg of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (i.e., WSC.HCl) was added thereto under ice-cooling and stirring. After stirring at room temperature for 5 hours, water was added and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with 0.5 N aqueous sodium hydroxide solution, 1 N hydrochloric acid and saturated brine, dried over magnesium sulfate, and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (dichloromethane:methanol=10:1), to give 9.24 mg of the title compound as pale yellow crystals.

^{1}H-NMR(400MHz, CD_3OD) δ 3.83 (3H, s), 3.98 (3H, s), 4.66 (2H, s), 7.03 (1H, s), 7.07-7.14 (2H, m), 7.34-7.43 (3H, m), 7.47 (1H, dt, J = 6.0, 8.0 Hz), 7.59-7.64 (1H, m), 7.72 (1H, d, J = 8.0 Hz), 7.89 (1H, s).

The compounds according to Examples II-228 to II-265 were synthesized by Synthesis Process II-A using the carboxylic acids produced in Production Examples II-31 and II-32, respectively.

EXAMPLE II-228

<u>7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid cyclopropylamide</u>

MS (ESI)m/z 314 MH^+

EXAMPLE II-229

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid cyclopropylmethylamide

MS (ESI)m/z 328 MH^+

EXAMPLE II-230

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid (2-methylsulfanylethyl)amide

MS (ESI)m/z 348 MH^+

EXAMPLE II-231

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methylpropyl]amide

MS (ESI)m/z 360 MH^+

EXAMPLE II-232

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid [(1*S*)-2-hydroxy-1-phenylethyl]amide

MS (ESI)m/z 394 MH^+

EXAMPLE II-233

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid [(2*R*)-tetrahydrofuran-2-ylmethyl]amide

MS (ESI)m/z 358 MH^+

EXAMPLE II-234

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid [(2*S*)-tetrahydrofuran-2-ylmethyl]amide

MS (ESI)m/z 358 MH^+

EXAMPLE II-235

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-3-methylsulfanylpropyl]amide

MS (ESI)m/z 392 MH^+

EXAMPLE II-236

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid (2-hydroxy-1-hydroxymethylethyl)amide

MS (ESI)m/z 348 MH^+

EXAMPLE II-237

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-3-methylbutyl]amide

MS (ESI)m/z 374 MH^-

EXAMPLE II-238

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid [(1*S*)-2-hydroxy-1-(1*H*-imidazol-4-ylmethyl)ethyl]amide

MS (ESI)m/z 398 MH^+

EXAMPLE II-239

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoylethyl]amide

MS (ESI)m/z 345 MH^+

EXAMPLE II-240

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid [(3*R*)-2-oxo-tetrahydrofuran-3-yl]amide

MS (ESI)m/z 358 MH^+

EXAMPLE II-241

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)amide

MS (ESI)m/z 354 MH^+

EXAMPLE II-242

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid (5-methylfuran-2-ylmethyl)amide

MS (ESI)m/z 368 MH^+

EXAMPLE II-243

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid (furan-3-ylmethyl)amide

MS (ESI)m/z 354 MH^+

EXAMPLE II-244

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid (benzo[*b*]furan-2-ylmethyl)amide

MS (ESI)m/z 404 MH^+

EXAMPLE II-245

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid (thiophen-2-ylmethyl)amide

MS (ESI)m/z 370 MH^+

EXAMPLE II-246

7-Fluoro-3-(3-fluorophenyl)-1*H*-indazole-5-carboxylic acid (pyridin-3-ylmethyl)amide

MS (ESI)m/z 365 MH^+

EXAMPLE II-247

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 346 MH^+

EXAMPLE II-248

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid cyclopropylmethylamide

MS (ESI)m/z 360 MH^+

EXAMPLE II-249

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (2-methylsulfanylethyl)amide

MS (ESI)m/z 380 MH^+

EXAMPLE II-250

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methylpropyl]amide

MS (ESI)m/z 392 MH^+

EXAMPLE II-251

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-2-hydroxy-1-phenylethyl]amide

MS (ESI)m/z 426 MH^+

EXAMPLE II-252

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(2*R*)-tetrahydrofuran-2-ylmethyl]amide

MS (ESI)m/z 390 MH^+

EXAMPLE II-253

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(2*S*)-tetrahydrofuran-2-ylmethyl]amide

MS (ESI)m/z 390 MH^+

EXAMPLE II-254

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-3-methylsulfanylpropyl]amide

MS (ESI)m/z 424 MH^+

EXAMPLE II-255

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (2-hydroxy-1-hydroxymethylethyl)amide

MS (ESI)m/z 380 MH^+

EXAMPLE II-256

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-3-methylbutyl]amide

MS (ESI)m/z 406 MH^+

EXAMPLE II-257

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-2-hydroxy-1-(1*H*-imidazol-4-ylmethyl)ethyl]amide

MS (ESI)m/z 430 MH^+

EXAMPLE II-258

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoylethyl]amide

MS (ESI)m/z 377 MH^+

EXAMPLE II-259

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(3*R*)-2-oxo-tetrahydrofuran-3-yl]amide

MS (ESI)m/z 390 MH^+

EXAMPLE II-260

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)amide

MS (ESI)m/z 386 MH^+

EXAMPLE II-261

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (5-methylfuran-2-ylmethyl)amide

MS (ESI)m/z 400 MH^+

EXAMPLE II-262

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (furan-3-ylmethyl)amide

MS (ESI)m/z 386 MH^-

EXAMPLE II-263

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (benzo[*b*]furan-2-ylmethyl)amide

MS (ESI)m/z 436 MH^+

EXAMPLE II-264

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (thiophen-2-ylmethyl)-amide

MS (ESI)m/z 402 MH^+

EXAMPLE II-265

7-Fluoro-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (pyridin-3-ylmethyl)amide

MS (ESI)m/z 397 MH^+

The compounds according to Examples II-266 and II-267 were synthesized by Synthesis Process II-D using the amines produced in Production Examples II-33 and II-34, respectively.

EXAMPLE II-266

N-(3-Benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-indazol-5-yl)-methanesulfonamide

MS (ESI)m/z 362 MH^+

EXAMPLE II-267

N-(4-Fluoro-3-naphthalen-2-yl-1H-indazol-5-yl)-methanesulfonamide

MS (ESI)m/z 356 MH^+

The compounds according to Examples II-268 to II-278 were synthesized by Synthesis Process II-B using the amines produced in Production Examples II-33 and II-34, respectively.

EXAMPLE II-268

Cyclopropanecarboxylic acid (3-benzo[b]thiophen-2-yl-4-fluoro-1H-indazol-5-yl)-amide

MS (ESI)m/z 352 MH^+

EXAMPLE II-269

(2S)-5-Oxo-pyrrolidine-2-carboxylic acid (3-benzo[b]thiophen-2-yl-4-fluoro-1H-indazol-5-yl)-amide

MS (ESI)m/z 395 MH^+

EXAMPLE II-270

Tetrahydrofuran-2-carboxylic acid (3-benzo[b]thiophen-2-yl-4-fluoro-1H-indazol-5-yl)-amide

MS (ESI)m/z 382 MH^+

EXAMPLE II-271

Furan-2-carboxylic acid (3-benzo[b]thiophen-2-yl-4-fluoro-1H-indazol-5-yl)-amide

MS (ESI)m/z 378 MH^+

EXAMPLE II-272

N-(3-Benzo[b]thiophen-2-yl-4-fluoro-1H-indazol-5-yl)-2-thiophen-2-yl-acetamide

MS (ESI)m/z 408 MH^+

EXAMPLE II-273

Thiophene-2-carboxylic acid (3-benzo[*b*]thiophen-2-yl-4-fluoro-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 394 MH^+

EXAMPLE II-274

Cyclopropanecarboxylic acid (4-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 346 MH^+

EXAMPLE II-275

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid (4-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 389 MH^+

EXAMPLE II-276

Tetrahydrofuran-2-carboxylic acid (4-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 376 MH^+

EXAMPLE II-277

Furan-2-carboxylic acid (4-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 372 MH^+

EXAMPLE II-278

N-(4-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-2-thiophen-2-yl-acetamide

MS (ESI)m/z 402 MH^+

The compounds according to Examples II-279 to II-282

were synthesized by Synthesis Process II-A using the carboxylic acid produced in Production Example II-35.

EXAMPLE II-279

3-Benzo[*b*]furan-2-yl-4-propoxy-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 376 MH^+

EXAMPLE II-280

3-Benzo[*b*]furan-2-yl-4-propoxy-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)amide

MS (ESI)m/z 416 MH^+

EXAMPLE II-281

3-Benzo[*b*]furan-2-yl-4-propoxy-1*H*-indazole-5-carboxylic acid ((1*S*)-1-hydroxymethyl-2-methyl-propyl)-amide

MS (ESI)m/z 422 MH^+

EXAMPLE II-282

3-Benzo[*b*]furan-2-yl-4-propoxy-1*H*-indazole-5-carboxylic acid ((1*S*)-2-hydroxy-1-phenyl-ethyl)-amide

MS (ESI)m/z 456 MH^+

The compounds according to Examples II-283 to II-315 were synthesized by Synthesis Process II-B using the amines produced in Production Examples II-36 through II-39, respectively.

EXAMPLE II-283

N-[7-Fluoro-3-(3-fluorophenyl)-1*H*-indazol-5-yl]acetamide

MS (ESI)m/z 288 MH^+

EXAMPLE II-284

(2*R*)-5-Oxo-pyrrolidine-2-carboxylic acid [7-fluoro-3-(3-fluorophenyl)-1*H*-indazol-5-yl]amide

MS (ESI)m/z 357 MH^+

EXAMPLE II-285

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid [7-fluoro-3-(3-fluorophenyl)-1*H*-indazol-5-yl]amide

MS (ESI)m/z 357 MH^+

EXAMPLE II-286

Tetrahydrofuran-3-carboxylic acid [7-fluoro-3-(3-fluorophenyl)-1*H*-indazol-5-yl]amide

MS (ESI)m/z 344 MH^+

EXAMPLE II-287

Tetrahydrofuran-2-carboxylic acid [7-fluoro-3-(3-fluorophenyl)-1*H*-indazol-5-yl]amide

MS (ESI)m/z 344 MH^+

EXAMPLE II-288

N-[7-Fluoro-3-(3-fluorophenyl)-1*H*-indazol-5-yl]-2-thiophen-3-ylacetamide

MS (ESI)m/z 370 MH^+

EXAMPLE II-289

N-[7-Fluoro-3-(3-fluorophenyl)-1*H*-indazol-5-yl]-2-thiophen-2-ylacetamide

MS (ESI)m/z 370 MH^+

EXAMPLE II-290

N-(7-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)acetamide

MS (ESI)m/z 320 MH^+

EXAMPLE II-291

Cyclopropylcarboxylic acid (7-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)amide

MS (ESI)m/z 346 MH^+

EXAMPLE II-292

(2*R*)-5-Oxo-pyrrolidine-2-carboxylic acid (7-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)amide

MS (ESI)m/z 389 MH^+

EXAMPLE II-293

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid (7-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)amide

MS (ESI)m/z 389 MH^+

EXAMPLE II-294

Tetrahydrofuran-3-carboxylic acid (7-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)amide

MS (ESI)m/z 376 MH^+

EXAMPLE II-295

Tetrahydrofuran-2-carboxylic acid (7-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)amide

MS (ESI)m/z 376 MH^+

EXAMPLE II-296

N-(7-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-2-thiophen-3-ylacetamide

MS (ESI)m/z 402 MH^+

EXAMPLE II-297

N-(7-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)-2-thiophen-

2-ylacetamide

MS (ESI)m/z 402 MH^+

EXAMPLE II-298

N-(4-Methoxy-3-naphthalen-2-yl-1*H*-indazol-5-yl)-acetamide

MS (ESI)m/z 332 MH^+

EXAMPLE II-299

Cyclopropanecarboxylic acid (4-methoxy-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 358 MH^+

EXAMPLE II-300

(2*R*)-5-Oxo-pyrrolidine-2-carboxylic acid (4-methoxy-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 401 MH^+

EXAMPLE II-301

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid (4-methoxy-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 401 MH^+

EXAMPLE II-302

Furan-2-carboxylic acid (4-methoxy-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 384 MH^+

EXAMPLE II-303

Thiophene-2-carboxylic acid (4-methoxy-3-naphthalen-2-yl-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 400 M^+

EXAMPLE II-304

N-(4-Methoxy-3-naphthalen-2-yl-1H-indazol-5-yl)-2-thiophen-2-yl-acetamide

MS (ESI)m/z 414 MH^+

EXAMPLE II-305

3-Methoxy-N-(4-methoxy-3-naphthalen-2-yl-1H-indazol-5-yl)propionamide

MS (ESI)m/z 376 MH^+

EXAMPLE II-306

3-Dimethylamino-N-(4-methoxy-3-naphthalen-2-yl-1H-indazol-5-yl)propionamide

MS (ESI)m/z 389 MH^+

EXAMPLE II-307

N-(3-Benzo[b]thiophen-2-yl-4-methoxy-1H-indazol-5-yl)-acetamide

MS (ESI)m/z 338 MH^+

EXAMPLE II-308

Cyclopropanecarboxylic acid (3-benzo[b]thiophen-2-yl-4-methoxy-1H-indazol-5-yl)-amide

MS (ESI)m/z 364 MH^+

EXAMPLE II-309

(2R)-5-Oxo-pyrrolidine-2-carboxylic acid (3-benzo[b]thiophen-2-yl-4-methoxy-1H-indazol-5-yl)-amide

MS (ESI)m/z 407 MH^+

EXAMPLE II-310

(2S)-5-Oxo-pyrrolidine-2-carboxylic acid (3-benzo[b]thiophen-2-yl-4-methoxy-1H-indazol-5-yl)-amide

MS (ESI)m/z 407 MH^+

EXAMPLE II-311

Furan-2-carboxylic acid (3-benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 390 MH^+

EXAMPLE II-312

Thiophene-2-carboxylic acid (3-benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazol-5-yl)-amide

MS (ESI)m/z 406 M^+

EXAMPLE II-313

N-(3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazol-5-yl)-2-thiophen-2-yl-acetamide

MS (ESI)m/z 420 MH^+

EXAMPLE II-314

N-(3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazol-5-yl)-3-methoxy-propionamide

MS (ESI)m/z 382 MH^+

EXAMPLE II-315

N-(3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazol-5-yl)-3-dimethylamino-propionamide

MS (ESI)m/z 395 MH^+

The compounds according to Examples II-316 to II-319 were synthesized by Synthesis Process II-C using the amine produced in Production Example II-40.

EXAMPLE II-316

N-(7-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-ylmethyl)-3-

methoxybenzamide

MS (ESI)m/z 426 MH^+

EXAMPLE II-317

N-(7-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-ylmethyl)-2-methoxybenzamide

MS (ESI)m/z 426 MH^+

EXAMPLE II-318

3-Cyano-*N*-(7-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-ylmethyl)benzamide

MS (ESI)m/z 421 MH^+

EXAMPLE II-319

3-Fluoro-*N*-(7-fluoro-3-naphthalen-2-yl-1*H*-indazol-5-ylmethyl)benzamide

MS (ESI)m/z 414 MH^+

The compounds according to Examples II-320 to II-323 were synthesized by Synthesis Process II-D using the amines produced in Production Examples II-36 through II-39, respectively.

EXAMPLE II-320

N-[7-Fluoro-3-(3-fluorophenyl)-1*H*-indazol-5-yl]methanesulfonamide

MS (ESI)m/z 324 MH^+

EXAMPLE II-321

N-(7-Fluoro-3-naphthalen-2-yl-1*H*-indazol-5-yl)methanesulfonamide

MS (ESI)m/z 356 MH^+

EXAMPLE II-322

N-(4-Methoxy-3-naphthalen-2-yl-1*H*-indazol-5-yl)-methanesulfonamide

MS (ESI)m/z 368 MH^+

EXAMPLE II-323

N-(3-Benzo[*b*]thiophen-2-yl-4-methoxy-1*H*-indazol-5-yl)-methanesulfonamide

MS (ESI)m/z 374 MH^+

The compounds according to Examples II-324 to II-340 were synthesized by Synthesis Process II-A using the carboxylic acids produced in Production Examples II-41 and II-42, respectively.

EXAMPLE II-324

6-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 358 MH^+

EXAMPLE II-325

6-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(3*R*)-2-oxo-tetrahydro-furan-3-yl]-amide

MS (ESI)m/z 402 MH^+

EXAMPLE II-326

6-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 398 MH^+

EXAMPLE II-327

6-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid

[(1*S*)-2-hydroxy-1-phenyl-ethyl]-amide

MS (ESI)m/z 438 MH^+

EXAMPLE II-328

6-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 404 MH^+

EXAMPLE II-329

6-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid cyclopropylmethylamide

MS (ESI)m/z 372 MH^+

EXAMPLE II-330

6-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (thiophen-2-ylmethyl)-amide

MS (ESI)m/z 414 M^+

EXAMPLE II-331

6-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid [(1*S*)-1-carbamoyl-ethyl]-amide

MS (ESI)m/z 389 MH^+

EXAMPLE II-332

6-Methoxy-3-naphthalen-2-yl-1*H*-indazole-5-carboxylic acid (tetrahydrofuran-2-ylmethyl)-amide

MS (ESI)m/z 402 MH^+

EXAMPLE II-333

3-Benzo[*b*]thiophen-2-yl-6-methoxy-1*H*-indazole-5-carboxylic acid cyclopropylamide

MS (ESI)m/z 364 MH^+

EXAMPLE II-334

3-Benzo[*b*]thiophen-2-yl-6-methoxy-1*H*-indazole-5-carboxylic acid [(3R)-2-oxo-tetrahydro-furan-3-yl]-amide

MS (ESI)m/z 408 MH^+

EXAMPLE II-335

3-Benzo[*b*]thiophen-2-yl-6-methoxy-1*H*-indazole-5-carboxylic acid (furan-2-ylmethyl)-amide

MS (ESI)m/z 404 MH^+

EXAMPLE II-336

3-Benzo[*b*]thiophen-2-yl-6-methoxy-1*H*-indazole-5-carboxylic acid [(1*S*)-2-hydroxy-1-phenyl-ethyl]-amide

MS (ESI)m/z 444 MH^+

EXAMPLE II-337

3-Benzo[*b*]thiophen-2-yl-6-methoxy-1*H*-indazole-5-carboxylic acid [(1*S*)-1-hydroxymethyl-2-methyl-propyl]-amide

MS (ESI)m/z 410 MH^+

EXAMPLE II-338

3-Benzo[*b*]thiophen-2-yl-6-methoxy-1*H*-indazole-5-carboxylic acid cyclopropylmethyl-amide

MS (ESI)m/z 378 MH^+

EXAMPLE II-339

3-Benzo[*b*]thiophen-2-yl-6-methoxy-1*H*-indazole-5-carboxylic acid (thiophen-2-ylmethyl)-amide

MS (ESI)m/z 420 MH^+

EXAMPLE II-340

3-Benzo[*b*]thiophen-2-yl-6-methoxy-1*H*-indazole-5-carboxylic

acid (tetrahydrofuran-2-ylmethyl)-amide

MS (ESI)m/z 408 MH^+

The compounds according to Examples II-341 to II-344 were synthesized by Synthesis Process II-B using the amine produced in Production Example II-43.

EXAMPLE II-341

Cyclopropanecarboxylic acid (3-benzo[*b*]furan-2-yl-4-fluoro-1*H*-indazole-5-yl)-amide

MS (ESI)m/z 336 MH^+

EXAMPLE II-342

(2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid (3-benzo[*b*]furan-2-yl-4-fluoro-1*H*-indazole-5-yl)-amide

MS (ESI)m/z 379 MH^+

EXAMPLE II-343

Furan-2-carboxylic acid (3-benzo[*b*]furan-2-yl-4-fluoro-1*H*-indazole-5-yl)-amide

MS (ESI)m/z 362 MH^+

EXAMPLE II-344

N-(3-Benzo[*b*]furan-2-yl-4-fluoro-1*H*-indazole-5-yl)-2-thiophen-2-yl-acetamide

MS (ESI)m/z 392 MH^+

The compounds (I) according to the present invention or a salt thereof exhibited an excellent action in tests for determining JNK inhibitory action. For example, the inhibitory actions on JNK 3 were as follows.

TEST EXAMPLE 1 Determination of JNK 3 Inhibition

Human JNK 3 was expressed as a fusion protein (GST-JNK 3) with glutathione S-transferase (GST) in *Escherichia coli* and was purified using glutathione Sepharose 4B beads. The amino acid sequence 1-169 of c-Jun was peppered as a fusion protein (GST-c-Jun) with GST in *Escherichia coli*, was purified using glutathione Sepharose 4B beads and was used as a substrate. A test compound was diluted with 100% dimethyl sulfoxide into 10 mM and was then further diluted with 10% aqueous dimethyl sulfoxide solution to yield a dilution series. To each well of 96-well OPTI plate (available from Packard) were placed 20 μl of the diluted compound, 30 μl of a substrate solution (1.2 μg of GST-c-Jun, 0.04 μg of GST-JNK 3, 0.2 μCi of [γ-^{33}P]ATP, 25 mM of HEPES pH=7.5, 10 mM of magnesium acetate, and 3.33 μM of ATP), and 50 μl of an enzyme solution (0.04 μg of GST-JNK 3, 25 mM of HEPES pH=7.5, and 10 mM magnesium acetate) up to 100 μl, and the mixture was allowed to react for 30 minutes. After terminating the reaction by adding 100 μl of a reaction terminator (80 mM ATP, 50 mg/ml glutathione SPA beads (available from Amersham Pharmacia Biotech)), the reaction mixture was shaken for 30 minutes. The mixture was centrifuged at room temperature at 1000 x *g* for 5 minutes, and the emission intensity thereof was determined on a TopCount™ illuminator (available from Packard). The activity is expressed by the 50% inhibitory concentration

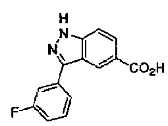
on the enzymatic activity of JNK, i.e., IC_{50} (nM).

Results: The compounds (I) according to the present invention or a salt thereof showed an excellent JNK 3-inhibitory activity. Examples of IC_{50} thereof will be shown below.

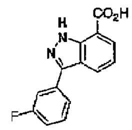
Ex. No.	IC_{50}	Ex. No.	IC_{50}
I-16	51nM	I-104	55nM
I-26	113nM	I-132	197nM
I-48	109nM	I-137	54nM
I-55	52nM	I-143	221nM
I-94	163nM	I-163	80nM
II-5	100nM	II-208	143nM
II-93	137nM	II-218	215nM
II-126	143nM	II-259	148nM
II-184	86nM	II-281	84nM
II-189	194nM	II-288	71nM

The structural formulae of the compounds according to Production examples and Examples will be listed below.

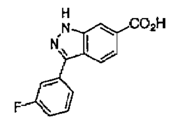
Production Example I-1-c



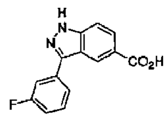
Production Example I-2-b



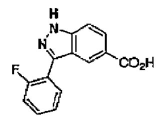
Production Example I-3-d



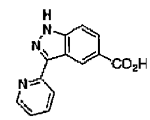
Production Example I-4-f



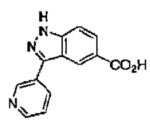
Production Example I-5-b



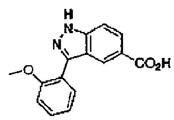
Production Example I-6-b



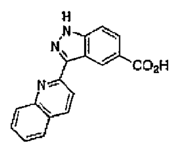
Production Example I-7-b



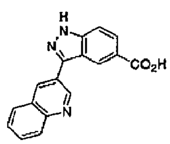
Production Example I-8-b



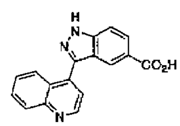
Production Example I-9-b



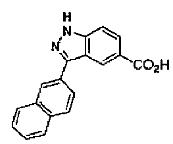
Production Example I-10-b



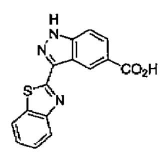
Production Example I-11-b



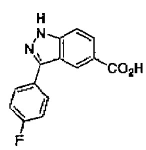
Production Example I-12-b



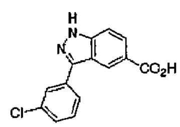
Production Example I-13-d



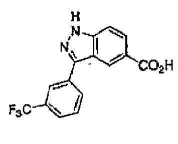
Production Example I-14-d



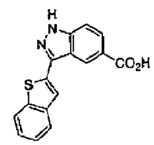
Production Example I-15-b



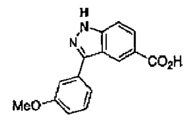
Production Example I-16-b



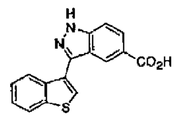
Production Example I-17-b



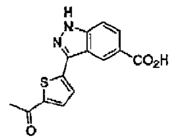
Production Example I-18-b



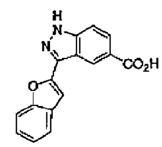
Production Example I-19-b



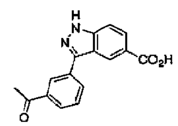
Production Example I-20-b



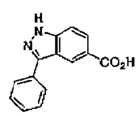
Production Example I-21-e



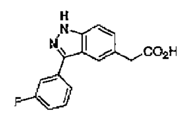
Production Example I-22-b



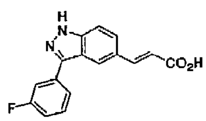
Production Example I-23-b



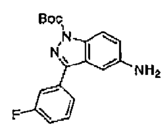
Production Example I-24-d



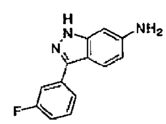
Production Example I-25-c



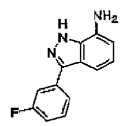
Production Example I-26-d



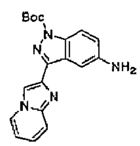
Production Example I-27-c



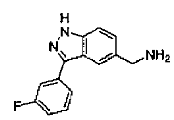
Production Example I-28-b



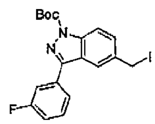
Production Example I-29-c



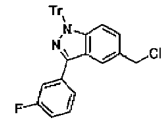
Production Example I-30-c



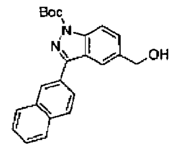
Production Example I-31



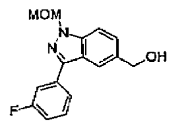
Production Example I-32-c



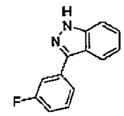
Production Example I-33



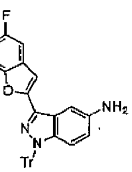
Production Example I-34



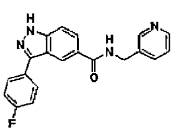
Production Example I-35-b



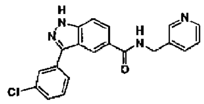
Production Example I-36-g



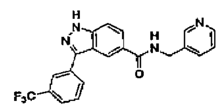
Example I-1



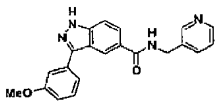
Example I-2



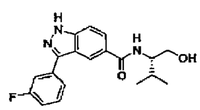
Example I-3



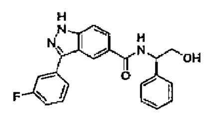
Example I-4



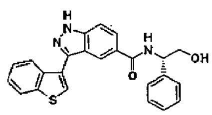
Example I-5



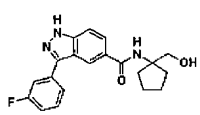
Example I-6



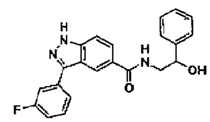
Example I-7



Example I-8

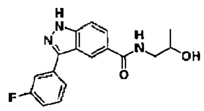


Example I-9

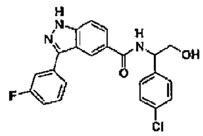


368

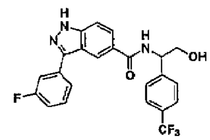
Example I-10



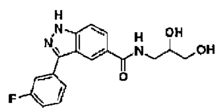
Example I-11



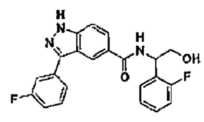
Example I-12



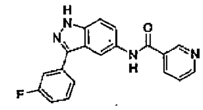
Example I-13



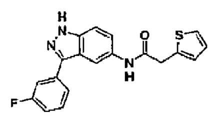
Example I-14



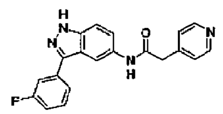
Example I-15



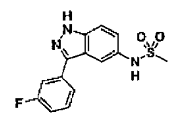
Example I-16



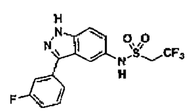
Example I-17



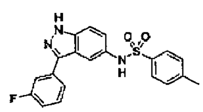
Example I-18



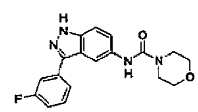
Example I-19



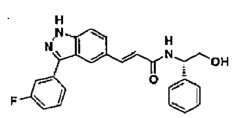
Example I-20



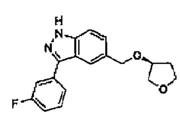
Example I-21



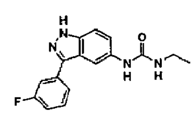
Example I-22



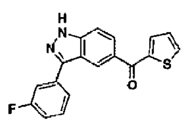
Example I-23



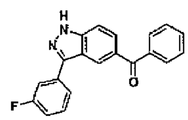
Example I-24



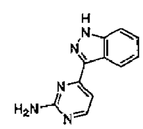
Example I-25



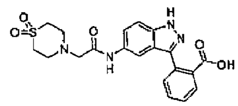
Example I-26



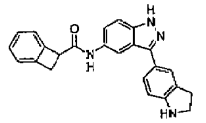
Example I-27



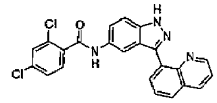
Example I-28



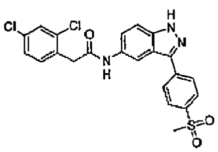
Example I-29



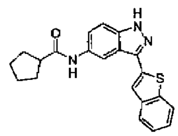
Example I-30



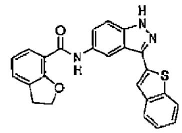
Example I-31



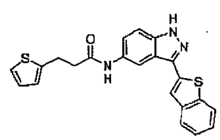
Example I-32



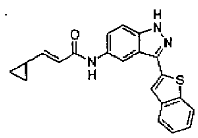
Example I-33



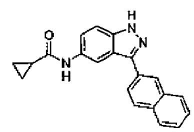
Example I-34



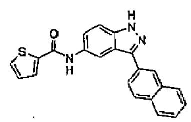
Example I-35



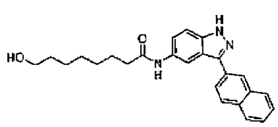
Example I-36



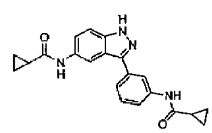
Example I-37



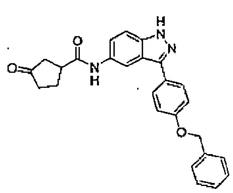
Example I-38



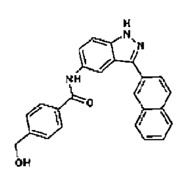
Example I-39



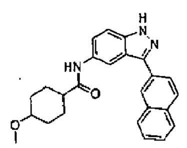
Example I-40



Example I-41

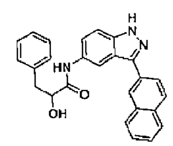


Example I-42

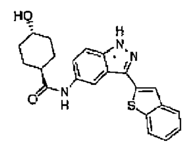


370

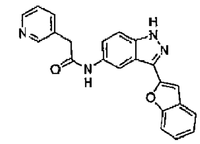
Example I-43



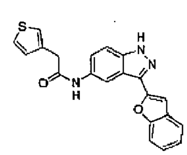
Example I-44



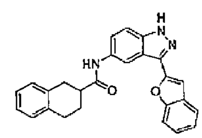
Example I-45



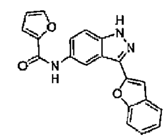
Example I-46



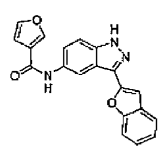
Example I-47



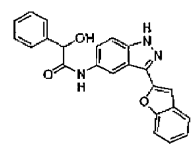
Example I-48



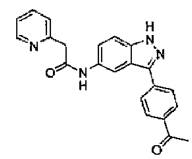
Example I-49



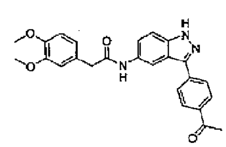
Example I-50



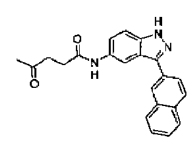
Example I-51



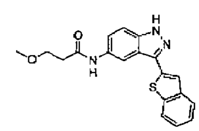
Example I-52



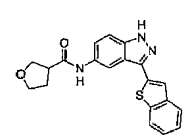
Example I-53



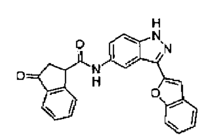
Example I-54



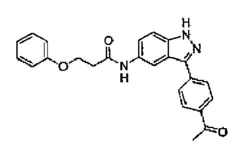
Example I-55



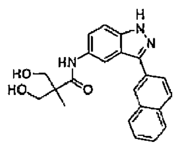
Example I-56



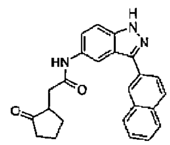
Example I-57



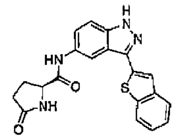
Example I-58



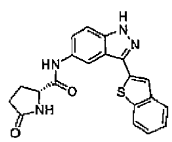
Example I-59



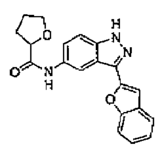
Example I-60



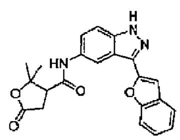
Example I-61



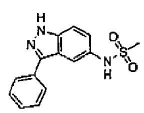
Example I-62



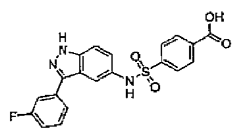
Example I-63



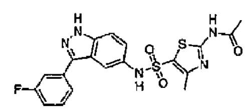
Example I-64



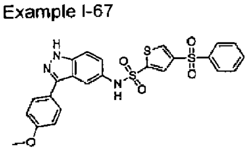
Example I-65



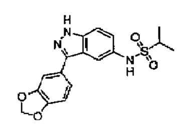
Example I-66



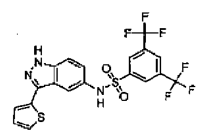
Example I-67



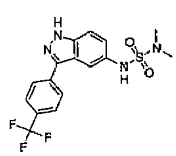
Example I-68



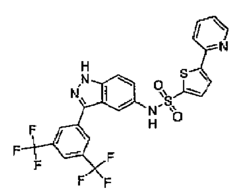
Example I-69



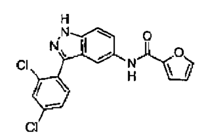
Example I-70



Example I-71

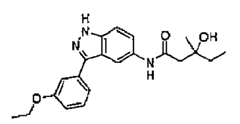


Example I-72

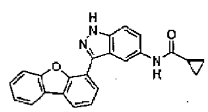


372

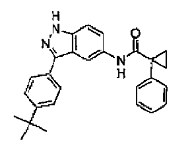
Example I-73



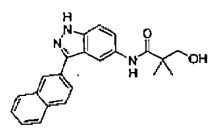
Example I-74



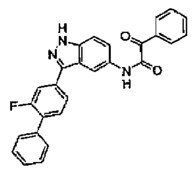
Example I-75



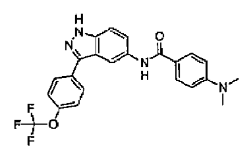
Example I-76



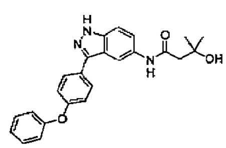
Example I-77



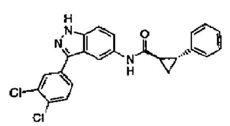
Example I-78



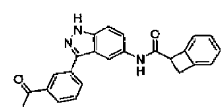
Example I-79



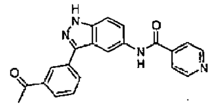
Example I-80



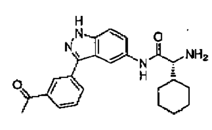
Example I-81



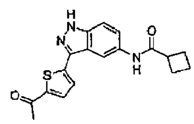
Example I-82



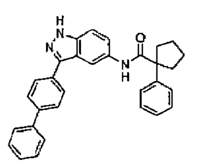
Example I-83



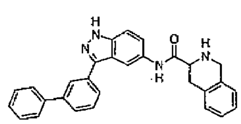
Example I-84



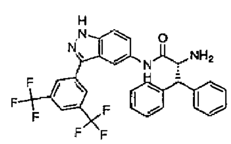
Example I-85



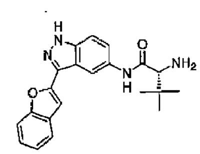
Example I-86



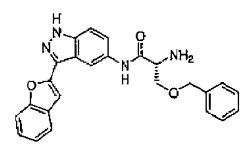
Example I-87



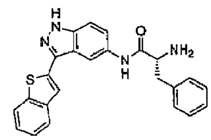
Example I-88



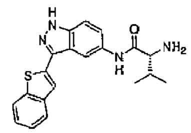
Example I-89



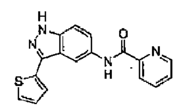
Example I-90



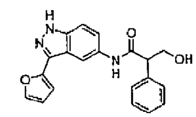
Example I-91



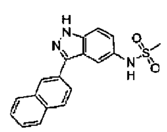
Example I-92



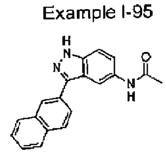
Example I-93



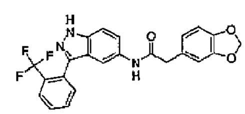
Example I-94



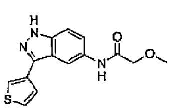
Example I-95



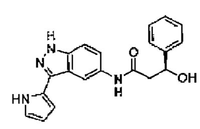
Example I-96



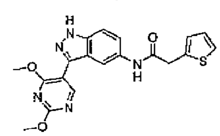
Example I-97



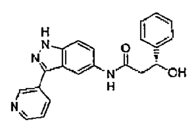
Example I-98



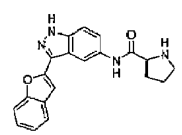
Example I-99



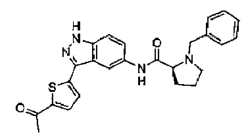
Example I-100



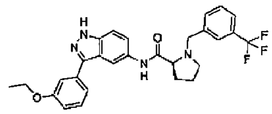
Example I-101



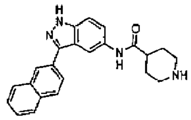
Example I-102



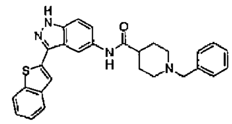
Example I-103



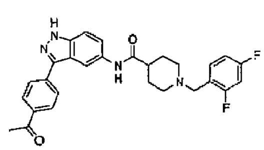
Example I-104



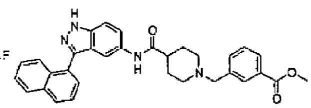
Example I-105



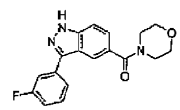
Example I-106



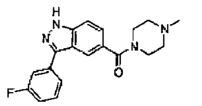
Example I-107



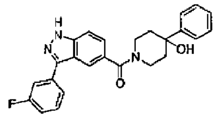
Example I-108



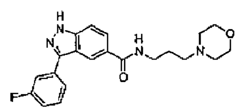
Example I-109



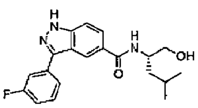
Example I-110



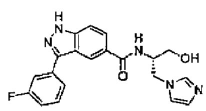
Example I-111



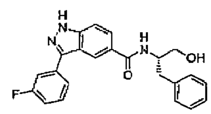
Example I-112



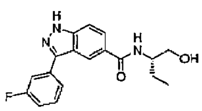
Example I-113



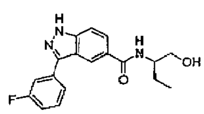
Example I-114



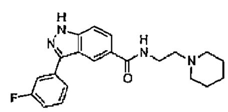
Example I-115



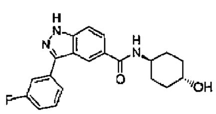
Example I-116



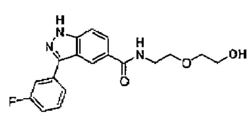
Example I-117



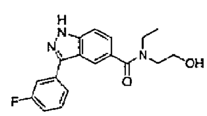
Example I-118



Example I-119

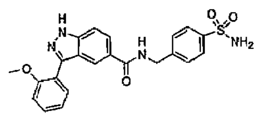


Example I-120

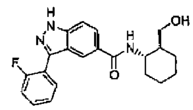


375

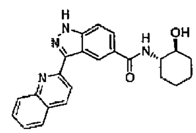
Example I-121



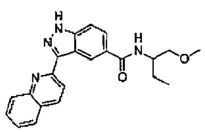
Example I-122



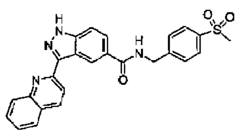
Example I-123



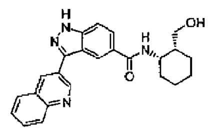
Example I-124



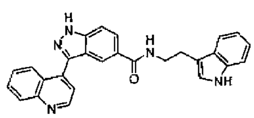
Example I-125



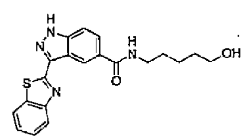
Example I-126



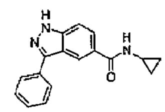
Example I-127



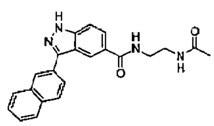
Example I-128



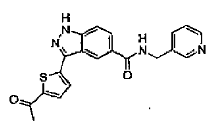
Example I-129



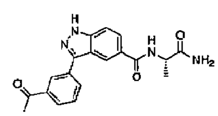
Example I-130



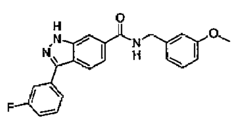
Example I-131



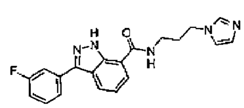
Example I-132



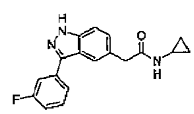
Example I-133



Example I-134

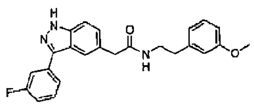


Example I-135

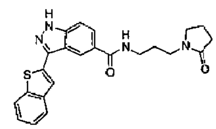


376

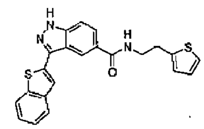
Example I-136



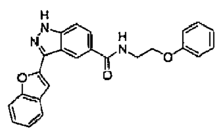
Example I-137



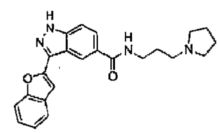
Example I-138



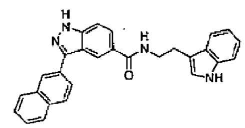
Example I-139



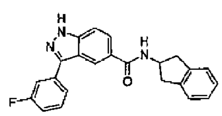
Example I-140



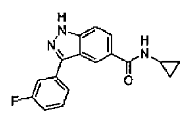
Example I-141



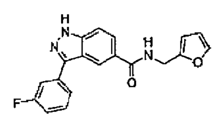
Example I-142



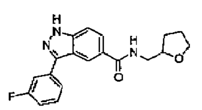
Example I-143



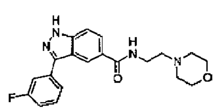
Example I-144



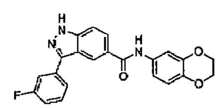
Example I-145



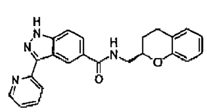
Example I-146



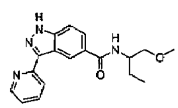
Example I-147



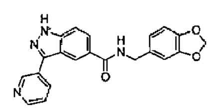
Example I-148



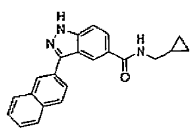
Example I-149



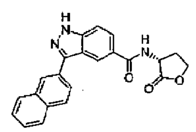
Example I-150



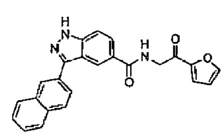
Example I-151



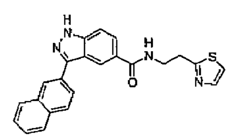
Example I-152



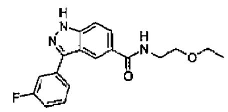
Example I-153



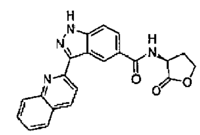
Example I-154



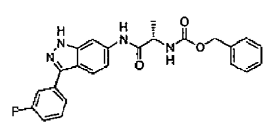
Example I-155



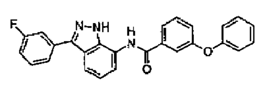
Example I-156



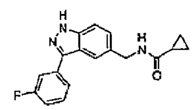
Example I-157



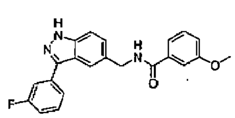
Example I-158



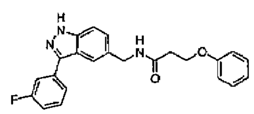
Example I-159



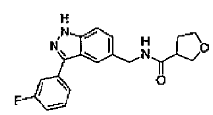
Example I-160



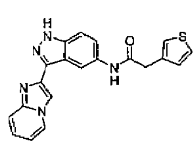
Example I-161



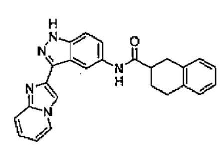
Example I-162



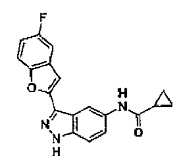
Example I-163



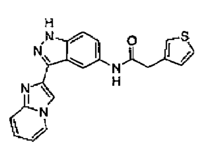
Example I-164



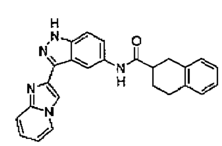
Example I-165



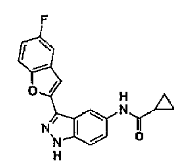
Example I-166



Example I-167

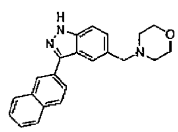


Example I-168

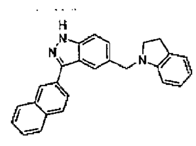


378

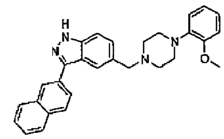
Example I-169



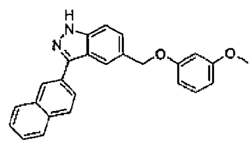
Example I-170



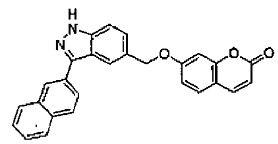
Example I-171



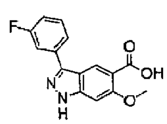
Example I-172



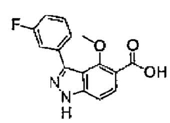
Example I-173



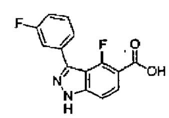
Production Example II-1-e



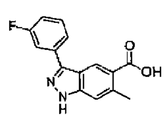
Production Example II-2-d



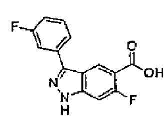
Production Example II-3-d



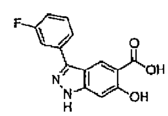
Production Example II-4-d



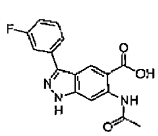
Production Example II-5-f



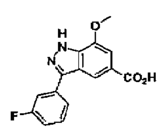
Production Example II-6



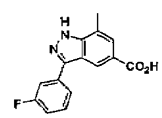
Production Example II-7-f



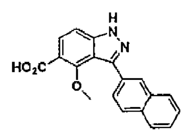
Production Example II-8-d



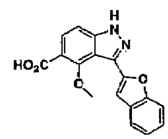
Production Example II-9-e



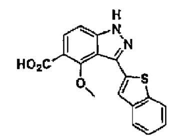
Production Example II-10-d



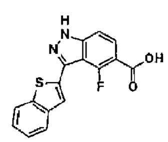
Production Example II-11-e



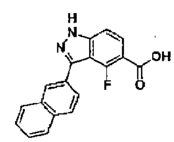
Production Example II-12-d



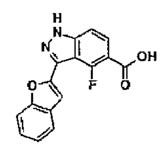
Production Example II-13-g



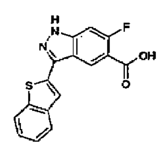
Production Example II-14-b



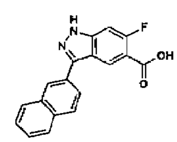
Production Example II-15-b



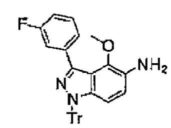
Production Example II-16-d



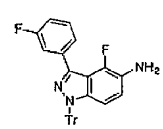
Production Example II-17-d



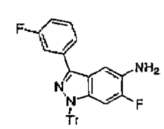
Production Example II-18-b



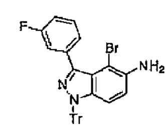
Production Example II-19-c



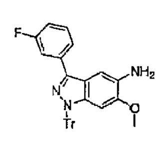
Production Example II-20-c



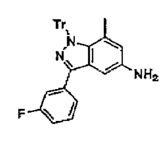
Production Example II-21



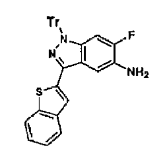
Production Example II-22-c



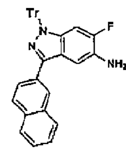
Production Example II-23



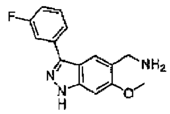
Production Example II-24-c



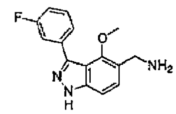
Production Example II-25-c



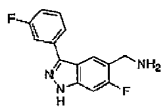
Production Example II-26



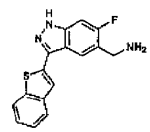
Production Example II-27-c



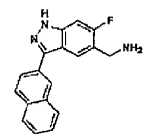
Production Example II-28



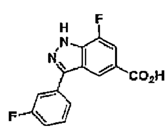
Production Example II-29



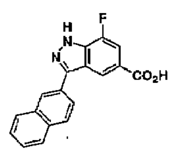
Production Example II-30



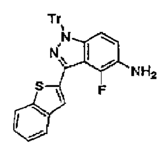
Production Example II-31-e



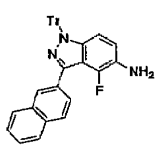
Production Example II-32-d



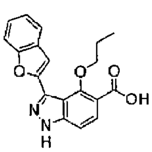
Production Example II-33-c



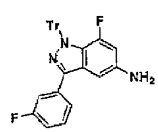
Production Example II-34-c



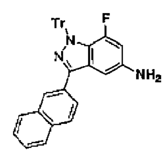
Production Example II-35-e



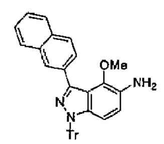
Production Example II-36-b



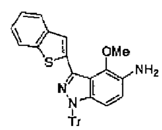
Production Example II-37-b



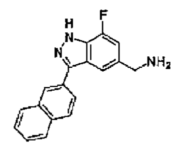
Production Example II-38-b



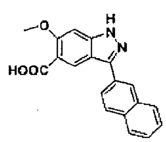
Production Example II-39-b



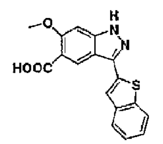
Production Example II-40



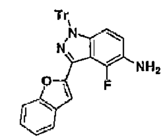
Production Example II-41-g



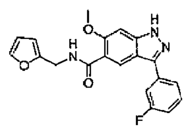
Production Example II-42-b



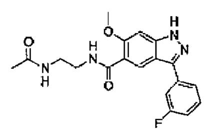
Production Example II-43-c



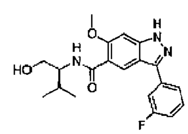
Example II-1



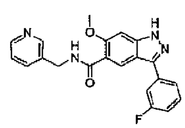
Example II-2



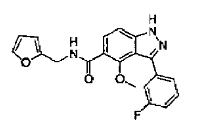
Example II-3



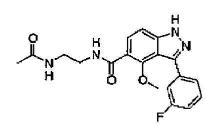
Example II-4



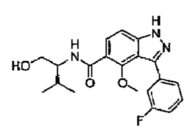
Example II-5



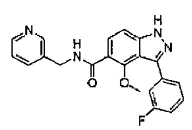
Example II-6



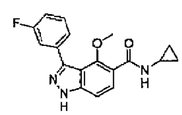
Example II-7



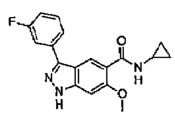
Example II-8



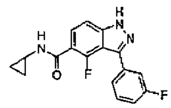
Example II-9



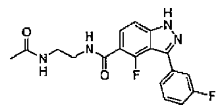
Example II-10



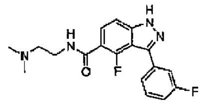
Example II-11



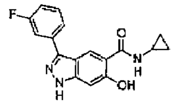
Example II-12



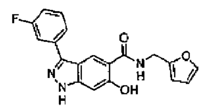
Example II-13



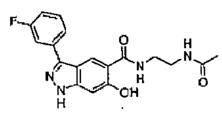
Example II-14



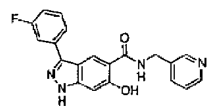
Example II-15



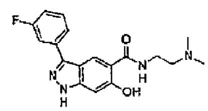
Example II-16



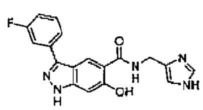
Example II-17



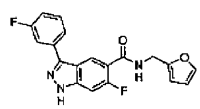
Example II-18



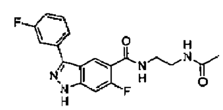
Example II-19



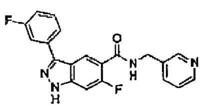
Example II-20



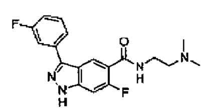
Example II-21



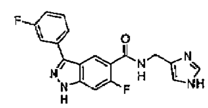
Example II-22



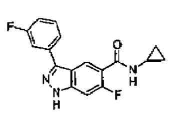
Example II-23



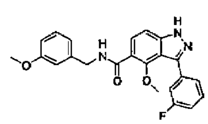
Example II-24



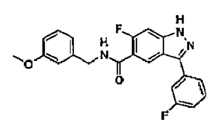
Example II-25



Example II-26

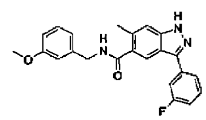


Example II-27

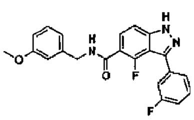


383

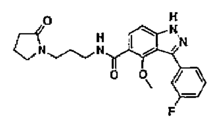
Example II-28



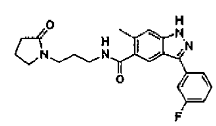
Example II-29



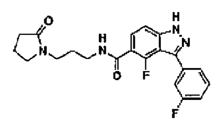
Example II-30



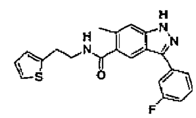
Example II-31



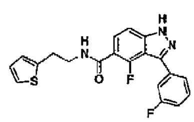
Example II-32



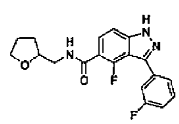
Example II-33



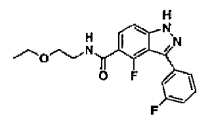
Example II-34



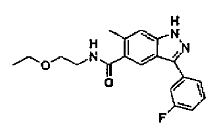
Example II-35



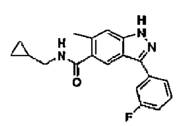
Example II-36



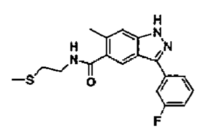
Example II-37



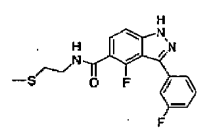
Example II-38



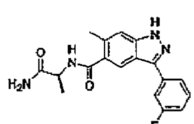
Example II-39



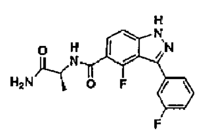
Example II-40



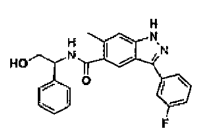
Example II-41



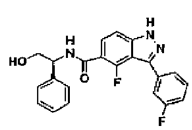
Example II-42



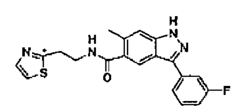
Example II-43



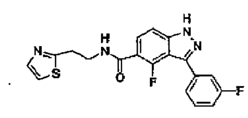
Example II-44



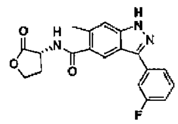
Example II-45



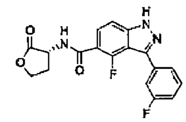
Example II-46



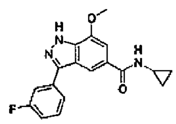
Example II-47



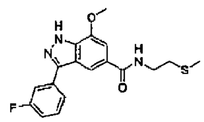
Example II-48



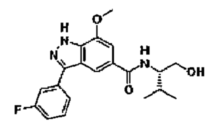
Example II-49



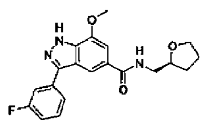
Example II-50



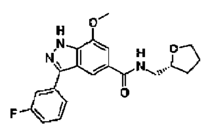
Example II-51



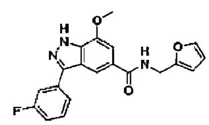
Example II-52



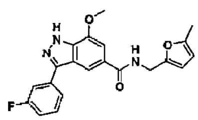
Example II-53



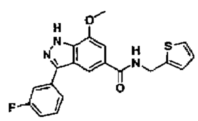
Example II-54



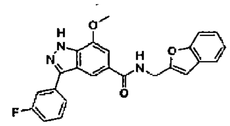
Example II-55



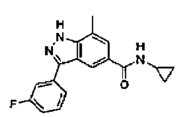
Example II-56



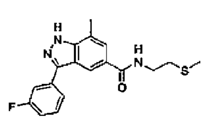
Example II-57



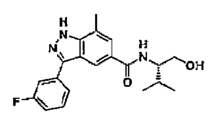
Example II-58



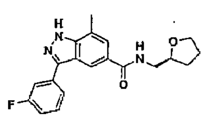
Example II-59



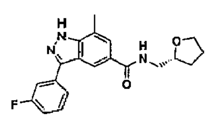
Example II-60



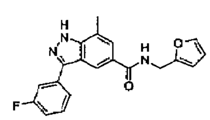
Example II-61



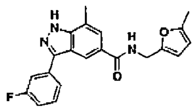
Example II-62



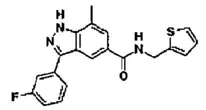
Example II-63



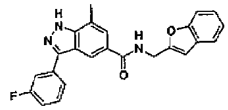
Example II-64



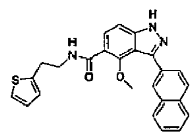
Example II-65



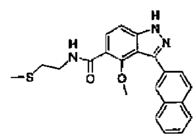
Example II-66



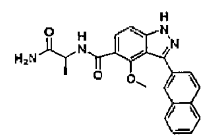
Example II-67



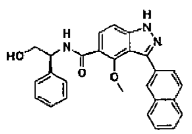
Example II-68



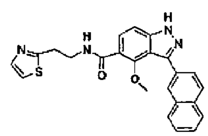
Example II-69



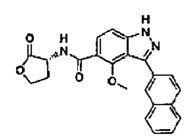
Example II-70



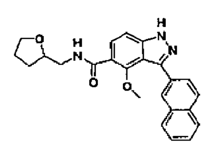
Example II-71



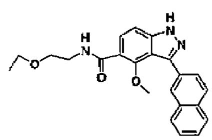
Example II-72



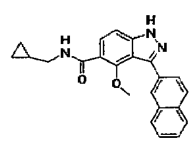
Example II-73



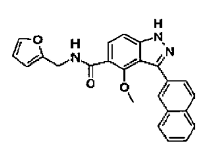
Example II-74



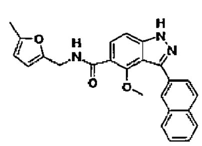
Example II-75



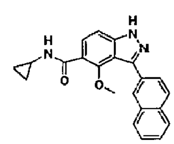
Example II-76



Example II-77

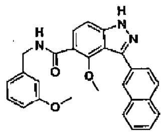


Example II-78

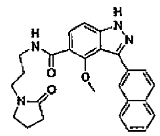


386

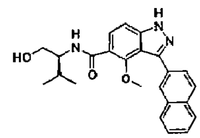
Example II-79



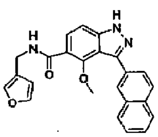
Example II-80



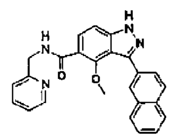
Example II-81



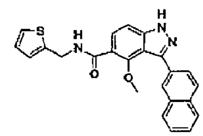
Example II-82



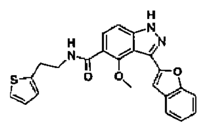
Example II-83



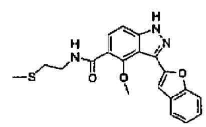
Example II-84



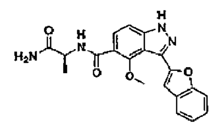
Example II-85



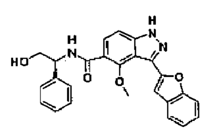
Example II-86



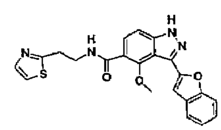
Example II-87



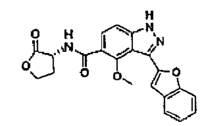
Example II-88



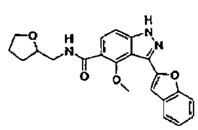
Example II-89



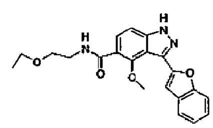
Example II-90



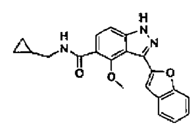
Example II-91



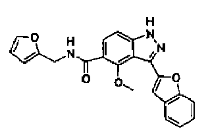
Example II-92



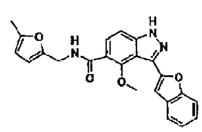
Example II-93



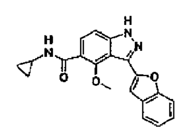
Example II-94



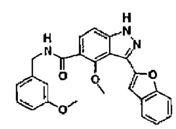
Example II-95



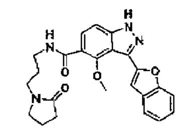
Example II-96



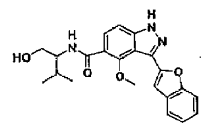
Example II-97



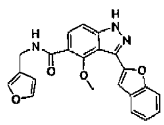
Example II-98



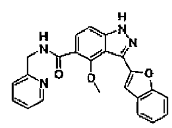
Example II-99



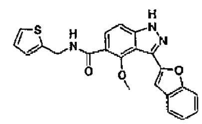
Example II-100



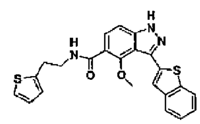
Example II-101



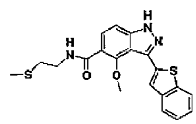
Example II-102



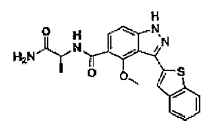
Example II-103



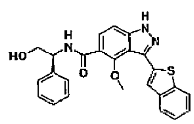
Example II-104



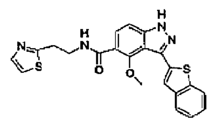
Example II-105



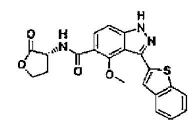
Example II-106



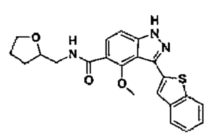
Example II-107



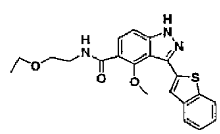
Example II-108



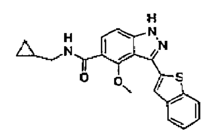
Example II-109



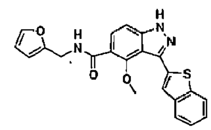
Example II-110



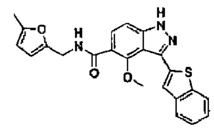
Example II-111



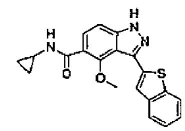
Example II-112



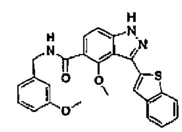
Example II-113



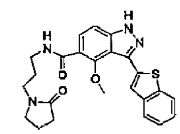
Example II-114



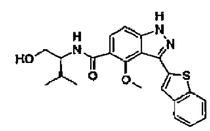
Example II-115



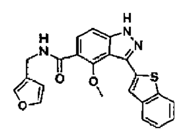
Example II-116



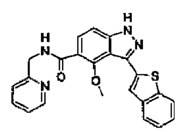
Example II-117



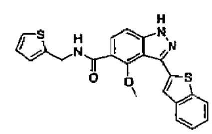
Example II-118



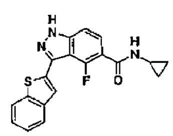
Example II-119



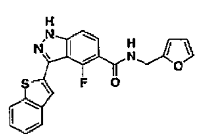
Example II-120



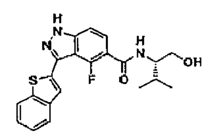
Example II-121



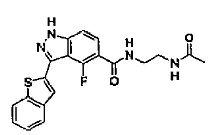
Example II-122



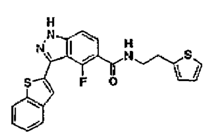
Example II-123



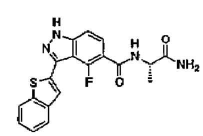
Example II-124



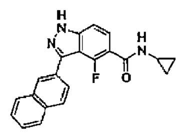
Example II-125



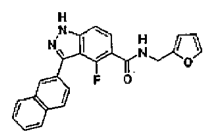
Example II-126



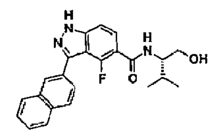
Example II-127



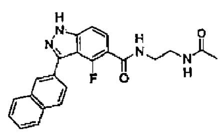
Example II-128



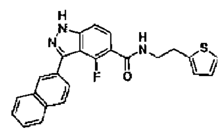
Example II-129



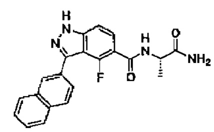
Example II-130



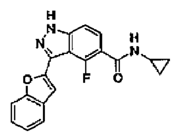
Example II-131



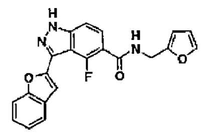
Example II-132



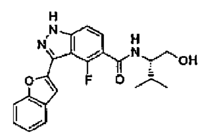
Example II-133



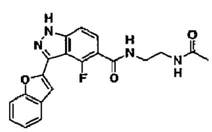
Example II-134



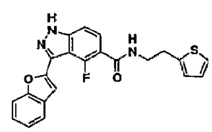
Example II-135



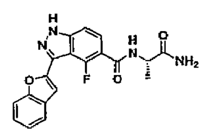
Example II-136



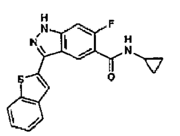
Example II-137



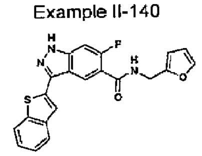
Example II-138



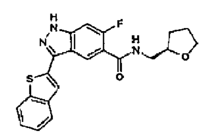
Example II-139



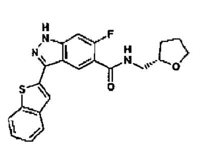
Example II-140



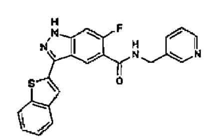
Example II-141



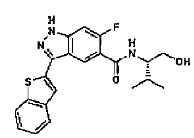
Example II-142



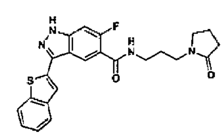
Example II-143



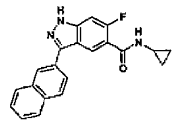
Example II-144



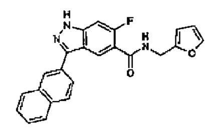
Example II-145



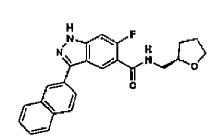
Example II-146



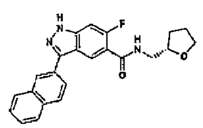
Example II-147



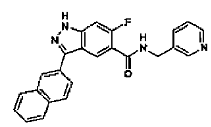
Example II-148



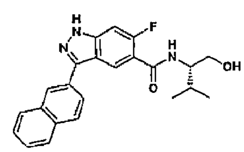
Example II-149



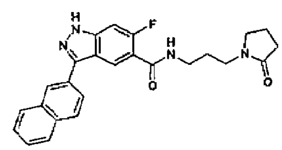
Example II-150



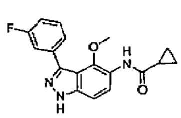
Example II-151



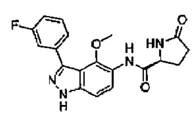
Example II-152



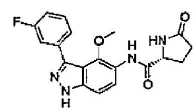
Example II-153



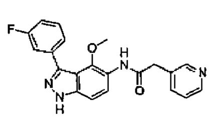
Example II-154



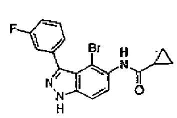
Example II-155



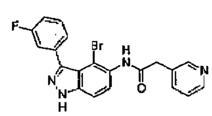
Example II-156



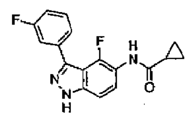
Example II-157



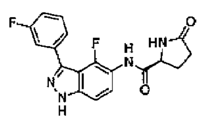
Example II-158



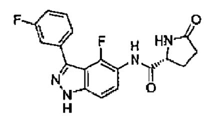
Example II-159



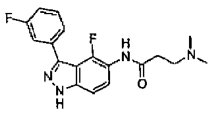
Example II-160



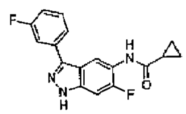
Example II-161



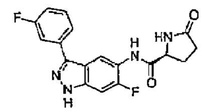
Example II-162



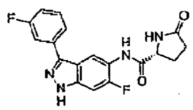
Example II-163



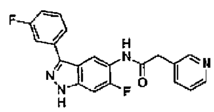
Example II-164



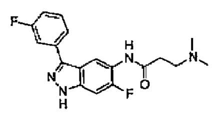
Example II-165



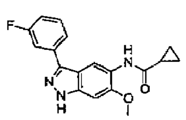
Example II-166



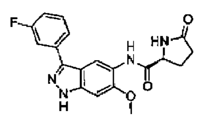
Example II-167



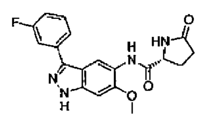
Example II-168



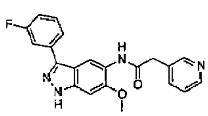
Example II-169



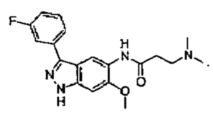
Example II-170



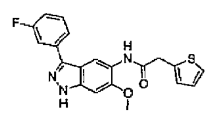
Example II-171



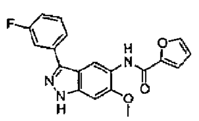
Example II-172



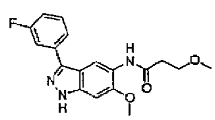
Example II-173



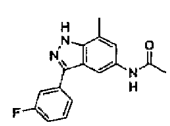
Example II-174



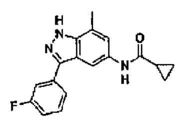
Example II-175



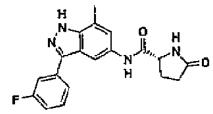
Example II-176



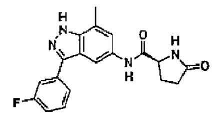
Example II-177



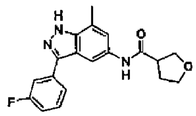
Example II-178



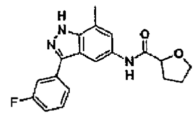
Example II-179



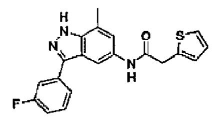
Example II-180



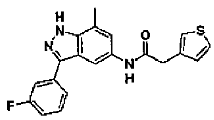
Example II-181



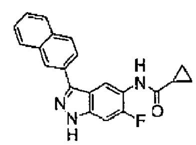
Example II-182



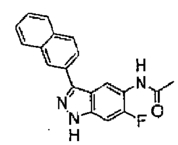
Example II-183



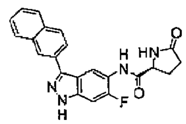
Example II-184



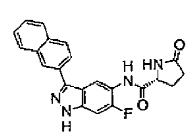
Example II-185



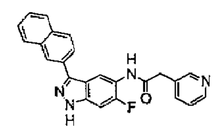
Example II-186



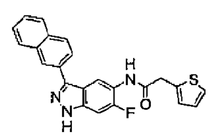
Example II-187



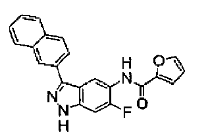
Example II-188



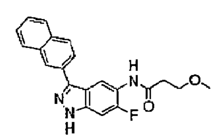
Example II-189



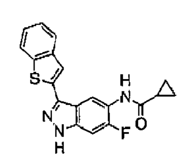
Example II-190



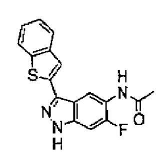
Example II-191



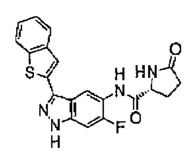
Example II-192



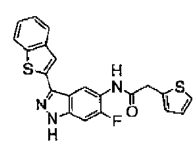
Example II-193



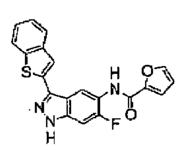
Example II-194



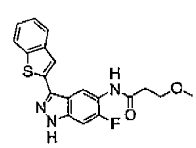
Example II-195



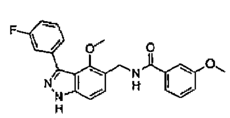
Example II-196



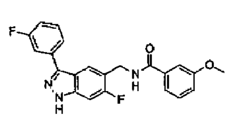
Example II-197



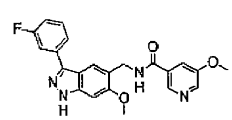
Example II-198



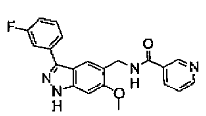
Example II-199



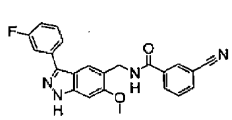
Example II-200



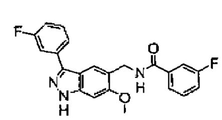
Example II-201



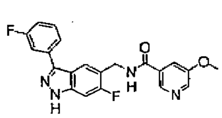
Example II-202



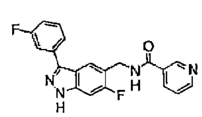
Example II-203



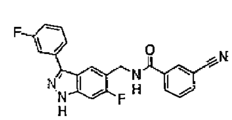
Example II-204



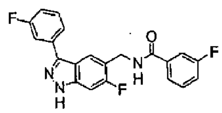
Example II-205



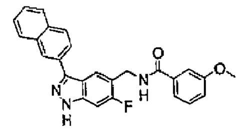
Example II-206



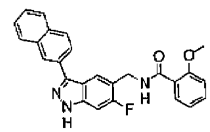
Example II-207



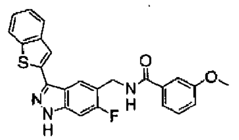
Example II-208



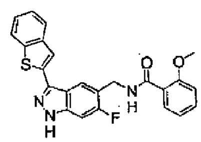
Example II-209



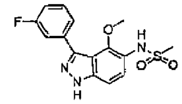
Example II-210



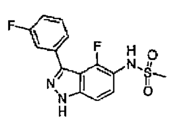
Example II-211



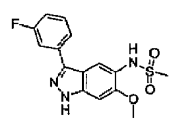
Example II-212



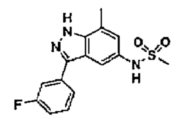
Example II-213



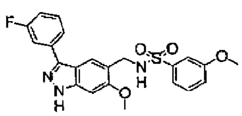
Example II-214



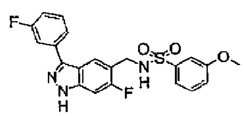
Example II-215



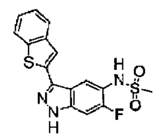
Example II-216



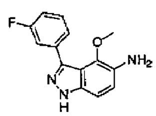
Example II-217



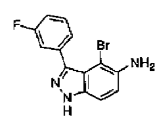
Example II-218



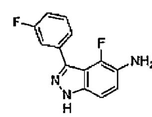
Example II-219



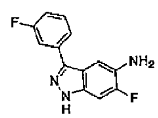
Example II-220



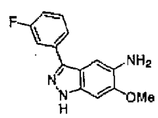
Example II-221



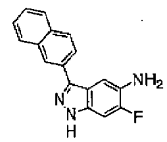
Example II-222



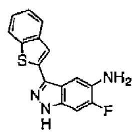
Example II-223



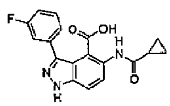
Example II-224



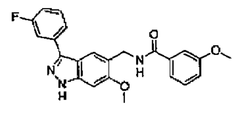
Example II-225



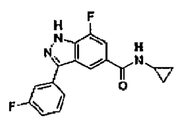
Example II-226-c



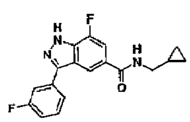
Example II-227



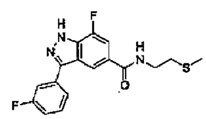
Example II-228



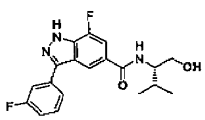
Example II-229



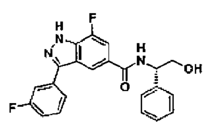
Example II-230



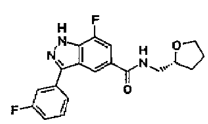
Example II-231



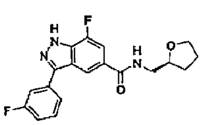
Example II-232



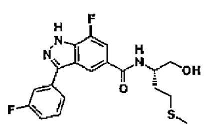
Example II-233



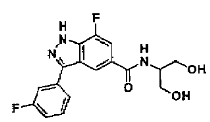
Example II-234



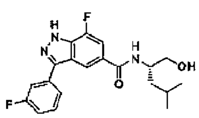
Example II-235



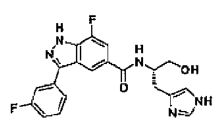
Example II-236



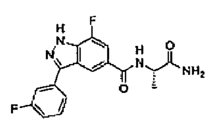
Example II-237



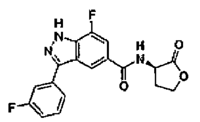
Example II-238



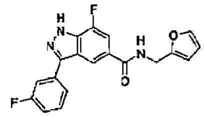
Example II-239



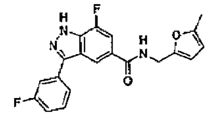
Example II-240



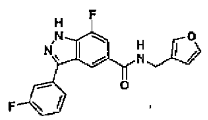
Example II-241



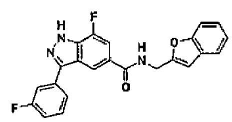
Example II-242



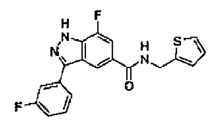
Example II-243



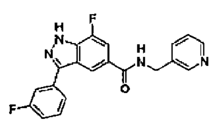
Example II-244



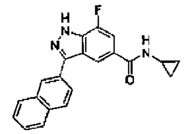
Example II-245



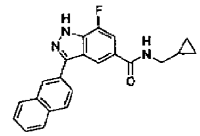
Example II-246



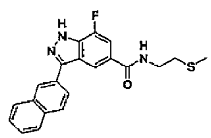
Example II-247



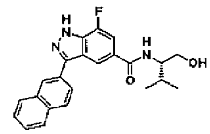
Example II-248



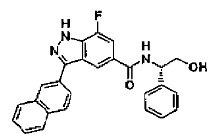
Example II-249



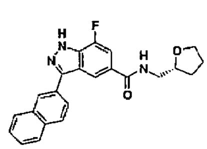
Example II-250



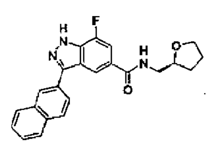
Example II-251



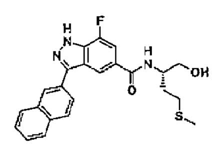
Example II-252



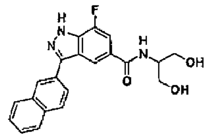
Example II-253



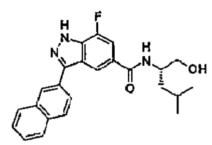
Example II-254



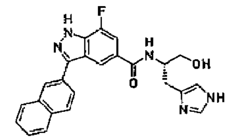
Example II-255



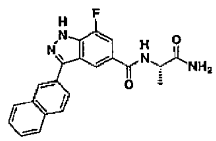
Example II-256



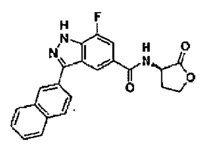
Example II-257



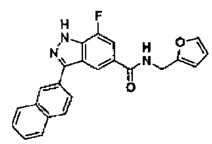
Example II-258



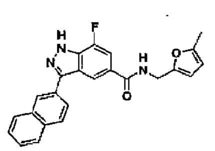
Example II-259



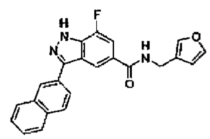
Example II-260



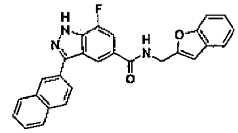
Example II-261



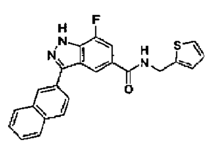
Example II-262



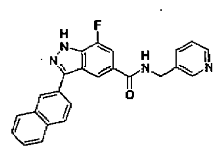
Example II-263



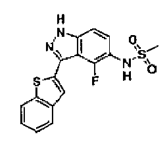
Example II-264



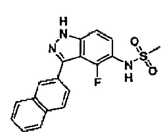
Example II-265



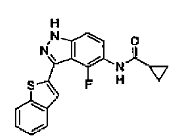
Example II-266



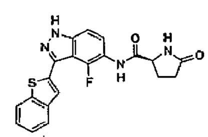
Example II-267



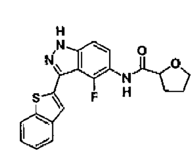
Example II-268



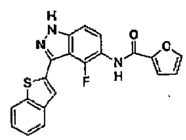
Example II-269



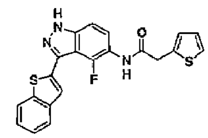
Example II-270



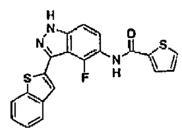
Example II-271



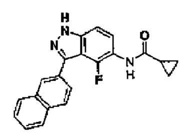
Example II-272



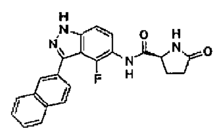
Example II-273



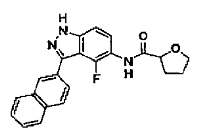
Example II-274



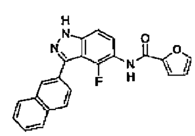
Example II-275



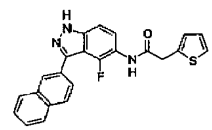
Example II-276



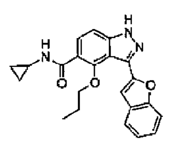
Example II-277



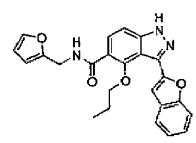
Example II-278



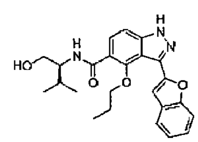
Example II-279



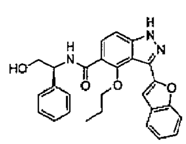
Example II-280



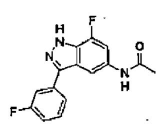
Example II-281



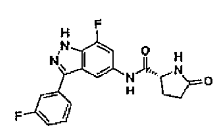
Example II-282



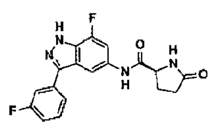
Example II-283



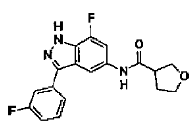
Example II-284



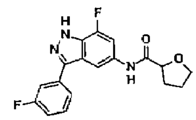
Example II-285



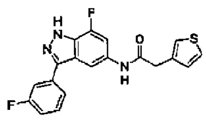
Example II-286



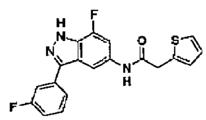
Example II-287



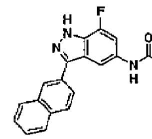
Example II-288



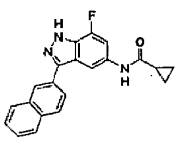
Example II-289



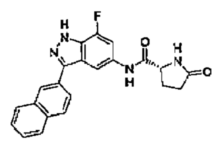
Example II-290



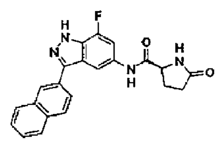
Example II-291



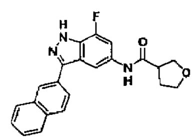
Example II-292



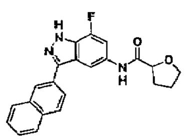
Example II-293



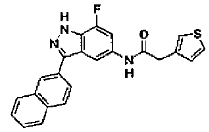
Example II-294



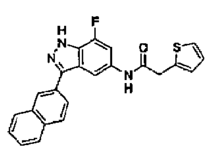
Example II-295



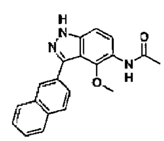
Example II-296



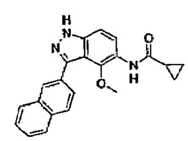
Example II-297



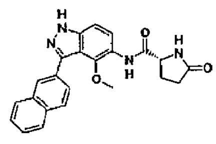
Example II-298



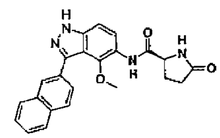
Example II-299



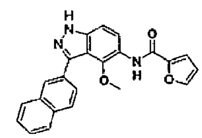
Example II-300



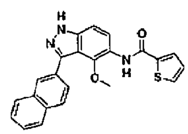
Example II-301



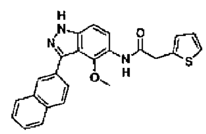
Example II-302



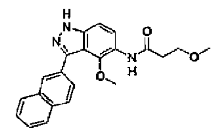
Example II-303



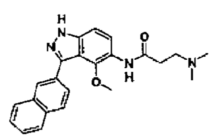
Example II-304



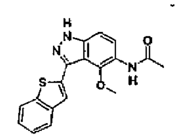
Example II-305



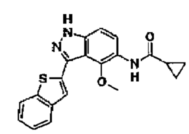
Example II-306



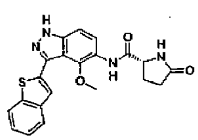
Example II-307



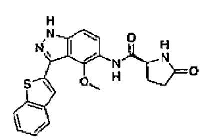
Example II-308



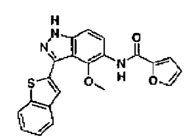
Example II-309



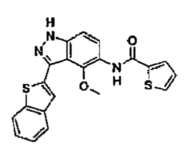
Example II-310



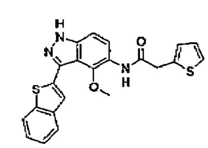
Example II-311



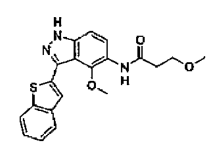
Example II-312



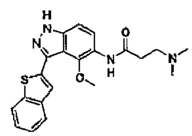
Example II-313



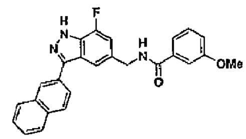
Example II-314



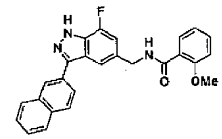
Example II-315



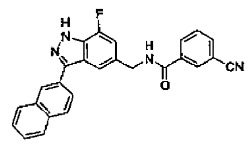
Example II-316



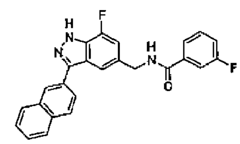
Example II-317



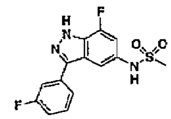
Example II-318



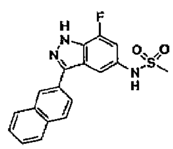
Example II-319



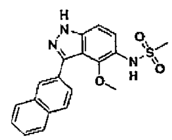
Example II-320



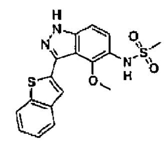
Example II-321



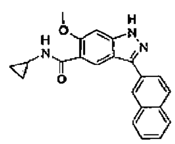
Example II-322



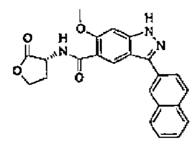
Example II-323



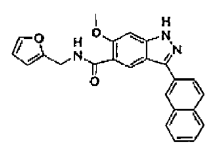
Example II-324



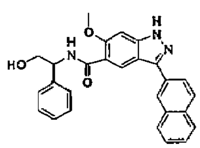
Example II-325



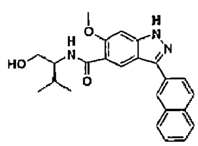
Example II-326



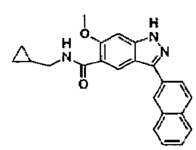
Example II-327



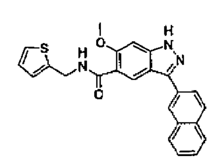
Example II-328



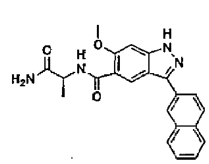
Example II-329



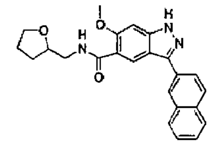
Example II-330



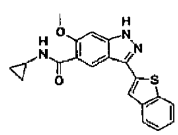
Example II-331



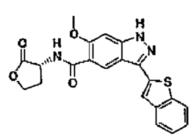
Example II-332



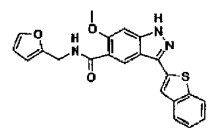
Example II-333



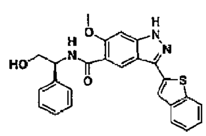
Example II-334



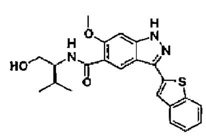
Example II-335



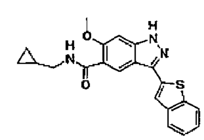
Example II-336



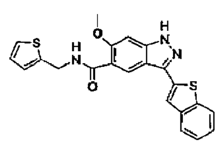
Example II-337



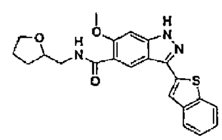
Example II-338



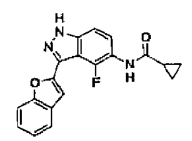
Example II-339



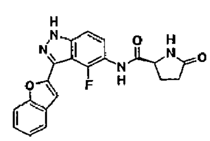
Example II-340



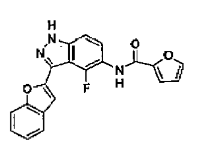
Example II-341



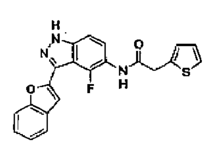
Example II-342



Example II-343



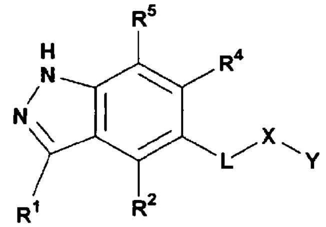
Example II-344



2002255263 23 Nov 2006

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound represented by the following formula, a salt thereof or a hydrate of them.



(I)

Wherein R^1 is a C_6-C_{14} aromatic cyclic hydrocarbon group which may be substituted or a 5- to 14-membered aromatic heterocyclic group which may be substituted;

R^2, R^4 and R^5 each independently represent a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a nitro group, a carboxyl group, a C_1-C_6 alkyl group which may be substituted, a C_1-C_6 alkoxy group which may be substituted, a C_2-C_7 acyl group which may be substituted, $-CO-NR^{2a}R^{2b}$, $-NR^{2b}CO-R^{2a}$ or $-NR^{2a}R^{2b}$ (wherein R^{2a} and R^{2b} each independently represent a hydrogen atom or a C_1-C_6 alkyl group which may be substituted), wherein at least one of R^2, R^4 and R^5 is not hydrogen;

L is a single bond, a C_1-C_6 alkylene group which may be substituted, a C_2-C_6 alkenylene group which may be substituted or a C_2-C_6 alkynylene group which may be substituted;

2002255263 23 Nov 2006

X is a group represented by $-CO-NR^8-V^2-$, NR^8-CO-V^2-, or $-NR^8-SO_2-V^2-$ (wherein R^8 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_1-C_6 alkyl group which may be substituted, a C_2-C_6 alkenyl group which may be substituted, a C_2-C_6 alkynyl group which may be substituted, a C_1-C_6 alkoxy group which may be substituted, a C_2-C_6 alkenyloxy group which may be substituted, a C_1-C_6 alkylthio group which may be substituted, a C_2-C_6 alkenylthio group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_3-C_8 cycloalkenyl group which may be substituted, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted, a C_6-C_{14} aromatic cyclic hydrocarbon group which may be substituted or a 5- to 14-membered aromatic heterocyclic group which may be substituted; and V^2 is a single bond or a C_1-C_6 alkylene group which may be substituted); and

Y is a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, a cyano group, a carboxyl group, a C_1-C_6 alkyl group which may be substituted, a C_2-C_6 alkenyl group which may be substituted, a C_2-C_6 alkynyl group which may be substituted, a C_1-C_6 alkoxy group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_3-C_8 cycloalkenyl group which may be substituted, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted, a C_6-C_{14} aromatic cyclic

hydrocarbon group which may be substituted, a 5- to 14-membered aromatic heterocyclic group which may be substituted, an amino group or $-W-R^{15}$ (wherein W is -CO- or $-SO_2-$; and R^{15} is a C_1-C_6 alkyl group which may be substituted, a C_6-C_{14} aromatic cyclic hydrocarbon group which may be substituted, a 5- to 14-membered aromatic heterocyclic group which may be substituted or an amino group).

2. The compound according to claim 1, a salt thereof or a hydrate of them, wherein R^2, R^4 and R^5 each independently represent a hydrogen atom, a halogen atom or a C_1-C_6 alkoxy group which may be substituted.

3. The compound according to claim 1 or 2, a salt thereof or a hydrate of them, wherein R^5 is a hydrogen atom.

4. The compound according to any one of claims 1 to 3, a salt thereof or a hydrate of them, wherein R^4 is a hydrogen atom.

5. The compound according to any one of claims 1 to 4, a salt thereof or a hydrate of them, wherein R^2 is a hydrogen atom.

6. The compound according to any one of claims 1 to 5, a salt thereof or a hydrate of them, wherein L is a single bond or a methylene group.

7. The compound according to any one of claims 1 to 5, a salt thereof or a hydrate of them, wherein L is a single bond.

8. The compound according to any one of claims 1 to 7, a salt thereof or a hydrate of them, wherein R^1 is a C_6-C_{14} aromatic cyclic hydrocarbon group or a 5- to 14-membered aromatic heterocyclic group; and R^1 is a group which may be substituted by one to three groups selected from the following Substituent Group "a".
<Substituent Group "a"> the group consisting of (1) (a) C_1-C_6 alkyl groups, (b) C_1-C_6 alkoxy groups, (c) C_1-C_7 acyl groups, (d) an amido group, (e) an amino group and (f) C_3-C_8 cycloalkyl groups, each of which may be substituted by one to three groups selected from the following Substituent Group "b", (2) halogen atoms, (3) a hydroxyl group, (4) a nitro group, (5) a cyano group, and (6) a carboxyl group;
<Substituent Group "b"> the group consisting of C_1-C_6 alkyl groups, halogen atoms, a hydroxyl group, a nitro group, a cyano group and a carboxyl group.

9. The compound according to any one of claims 1 to 7, a salt thereof or a hydrate of them, wherein R^1 is a phenyl group, a naphthyl group or a 5- to 10- aromatic heterocyclic group; and R^1 is a group which may be substituted by one to three groups selected from the Substituent Group "a" as described in claim 9.

10. The compound according to any one of claims 1 to 7, a salt thereof or a hydrate of them, wherein R^1 is a phenyl group, 2-naphthyl group, pyridyl group, 2-thienyl group, 2-furyl group, 2-benzofuryl group, 2-quinolyl group

or 2-benzothienyl group; and R^1 is a group which may be substituted by one to three groups selected from the Substituent Group "a" described in claim 9.

11. The compound according to any one of claims 1 to 7, a salt thereof or a hydrate of them, wherein R^1 is a 2-naphthyl group, 2-benzofuryl group or 2-benzothienyl group; and R^1 is a group which may be substituted by one to three groups selected from the Substituent Group "a" as described in claim 9.

12. The compound according to any one of claims 8 to 11, a salt thereof or a hydrate of them, wherein the Substituent Group "a" is the group consisting of (1) C_1-C_6 alkyl groups which may be substituted by one to three groups selected from the group consisting of a halogen atom, a hydroxyl group and a cyano group, (2) C_1-C_6 alkoxy groups which may be substituted by one to three groups selected from the group consisting of a halogen atom, a hydroxyl group and a cyano group, (3) halogen atoms, (4) a hydroxyl group, and (5) a cyano group.

13. The compound according to any one of claims 8 to 11, a salt thereof or a hydrate of them, wherein the Substituent Group "a" is halogen atoms.

14. The compound according to claim 1, a salt thereof or a hydrate of them, wherein R^8 is a hydrogen atom.

15. The compound according to any one of claims 1 to 13, a salt thereof or a hydrate of them, wherein X is a

group represented by $-CO-NH-(CH_2)_t-$ (wherein t is 0 or 1).

16. The compound according to any one of claims 1 to 13, a salt thereof or a hydrate of them, wherein X is a group represented by $-NH-CO-(CH_2)_t-$ (wherein t is 0 or 1).

17. The compound according to any one of claims 1 to 16, a salt thereof or a hydrate of them, wherein Y is a C_1-C_6 alkyl group, a C_6-C_{14} aromatic cyclic hydrocarbon group, a C_1-C_6 alkoxy group, a C_3-C_8 cycloalkyl group, a 5- to 14-membered non-aromatic heterocyclic group and a 5- to 14-membered aromatic heterocyclic group, and Y is a group which may be substituted by one to three groups selected from the following Substituent Group "a2".

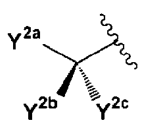
<Substituent Group "a2"> the group consisting of (1) (a) C_1-C_6 alkyl groups, (b) C_2-C_6 alkenyl groups, (c) C_2-C_6 alkynyl groups, (d) C_1-C_6 alkoxy groups, (e) C_2-C_7 acyl groups, (f) an amide group, (g) an amino group, (h) a C_3-C_8 cycloalkyl group, (i) C_3-C_8 cycloalkenyl groups, (j) C_6-C_{14} aromatic cyclic hydrocarbon groups, (k) 5- to 14-membered aromatic heterocyclic groups, (l) C_6-C_{14} aryloxy groups, and (m) 5- to 14-membered non-aromatic heterocyclic groups, each of which may be substituted by one to three groups selected from the following Substituent Group "b2", (2) halogen atoms, (3) a hydroxyl group, (4) a nitro group, (5) a cyano group, and (6) a carboxyl group;

<Substituent Group "b2"> the group consisting of C_1-C_6 alkyl groups, halogen atoms, a hydroxyl group, a nitro

group, a cyano group, and a carboxyl group.

18. The compound according to any one of claims 1 to 17, a salt thereof or a hydrate of them, wherein Y is a C_3-C_8 cycloalkyl group, a phenyl group, a 5- or 6-membered non-aromatic heterocyclic group or a 5- or 6-membered aromatic heterocyclic group, and Y is a group which may be substituted by one to three groups selected from the Substituent Group "a2" as described in claim 17.

19. The compound according to any one of claims 1 to 17, a salt thereof or a hydrate of them, wherein Y is a furyl group, a thienyl group, a pyrrolyl group, a phenyl group, a pyridyl group, a C_3-C_8 cycloalkyl group, a tetrahydrofuran-yl group, a tetrahydrothiophenyl group, a pyrrolidinyl group, a tetrahydrofuran-2-one-yl group, a pyrrolidin-2-one-yl group or a group represented by the formula:



(wherein Y^{2a} is a group represented by $-CONH_2$ or $-CH_2OH$; and Y^{2b} and Y^{2c} each independently represent a hydrogen atom, a phenyl group which may be substituted or a C_1-C_6 alkyl group which may be substituted), and wherein Y is a group which may be substituted by one to three groups selected from the Substituent Group "a2" as described in claim 17.

20. The compound according to any one of claims 1 to 17, a salt thereof or a hydrate of them, wherein Y is a furyl group or a thienyl group; and Y is a group which may be substituted by one to three groups selected from the Substituent Group "a2" as described in claim 17.

21. The compound according to any one of claims 17 to 20, a salt thereof or a hydrate of them, wherein the Substituent Group "a2" is the group consisting of (1) (a) C_1-C_6 alkyl groups, (b) C_1-C_6 alkoxy groups, (c) C_1-C_7 acyl groups, (d) an amide group, (e) an amino group, and (f) C_3-C_8 cycloalkyl groups, each of which may be substituted by one to three groups selected from the following Substituent Group "b2", (2) halogen atoms, (3) a hydroxyl group, (4) a nitro group, (5) a cyano group, and (6) a carboxyl group, and the Substituent Group "b2" is the group consisting of C_1-C_6 alkyl groups, halogen atoms, a hydroxyl group, a nitro group, a cyano group, and a carboxyl group.

22. The compound according to any one of claims 17 to 20, a salt thereof or a hydrate of them, wherein the Substituent Group "a2" is the group consisting of (1) C_1-C_6 alkoxy groups, (2) halogen atoms, and (3) a cyano group.

23. A pharmaceutical composition comprising the compound according to claim 1, a salt thereof or a hydrate of them, and a pharmacologically acceptable carrier.

24. A c-Jun amino-terminal kinase (JNK) inhibitor, comprising the compound according to claim 1, a salt

thereof or a hydrate of them.

25. c-Jun amino-terminal kinase 1 (JNK 1), c-Jun amino-terminal kinase 2 (JNK 2) and/or c-Jun amino-terminal kinase 3 (JNK 3) inhibitors, comprising the compound according to claim 1, a salt thereof or a hydrate of them.

26. An agent for treating or preventing an immunological disease or inflammatory disease, comprising the compound according to claim 1, a salt thereof or a hydrate of them.

27. An agent for treating or preventing neurodegenerative disease, comprising the compound according to claim 1, a salt thereof or a hydrate of them.

28. An agent for treating or preventing Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis or spinocerebellar degeneration, comprising the compound according to claim 1, a salt thereof or a hydrate of them.

29. Use of the compound according to claim 1, a salt thereof or a hydrate of them, for therapy or prophylaxis of an immunological disease, inflammatory disease and/or neurodegenerative disease.

30. Use of the compound according to claim 1, a salt thereof or a hydrate of them, for producing an agent for treating or preventing a disease against which inhibition of a c-Jun amino-terminal kinase (JNK) is effective, an immunological disease, an inflammatory disease or a

neurodegenerative disease.

31. The use according to claim 30, wherein the disease is Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis or spinocerebellar degeneration.

32. A method for treating or preventing a disease against which inhibition of c-Jun amino-terminal kinase 3 (JNK 3) is effective, an immunological disease, an inflammatory disease and/or a neurodegenerative disease, which comprises administering a pharmacologically effective amount of the compound according to claim 1, a salt thereof or a hydrate of them to a patient.

33. A method for treating or preventing a disease against which inhibition of a c-Jun amino-terminal kinase (JNK) is effective, an immunological disease, an inflammatory disease or a neurodegenerative disease, which comprises administering a pharmacologically effective amount of the compound according to claim 1, a salt thereof or a hydrate of them to a patient.

34. The method according to claim 35, wherein the disease is Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis or spinocerebellar degeneration.

35. Use of the compound according to claim 1, a salt thereof or a hydrate of them, for producing an agent for treating or preventing a disease against which inhibition

2002255263 23 Nov 2006

of a c-Jun amino-terminal kinase 3 (JNK 3) is effective, an immunological disease, an inflammatory disease or a neurodegenerative disease.

36. A compound according to claim 1, as hereinbefore described with reference to the Examples.

37. A composition according to claim 23, substantially as hereinbefore described.

38. An agent according to any one of claims 26, 27 or 28, substantially as hereinbefore described.

39. A use according to claim 30 or claim 31, substantially as hereinbefore described.

40. A method according to any one of claims 32 to claim 34, substantially as hereinbefore described.